
Effects of hormone treatment
on sexual functioning
in postmenopausal women
pharmacological intervention and
female sexuality: a complex,
controversial clinical and social issue

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Effects of hormone treatment on sexual functioning in postmenopausal women

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Opgedragen aan Chetty ter Kuile

CONTENTS

INTRODUCTION AND SCOPE OF THE THESIS

The studies presented in this thesis have been conducted to investigate the effects of hormone therapy (HT) and tibolone on sexual function in postmenopausal women. The reason for initiating research into these effects has been the growing off-label use of tibolone by postmenopausal women experiencing sexual problems. Sufficient evidence for the effects of tibolone on sexual function and dysfunction in postmenopausal women is not available, but as tibolone does have some androgenic properties, the theory that it may therefore work as a weak androgen justifies pharmacological intervention in daily clinical practice. Thus, the main objective of this thesis has been to determine the effects of conventional hormone therapy (oestrogen and progesterone), and tibolone in particular, on sexual function in postmenopausal women with female sexual dysfunction (FSD).

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CHAPTER 1

Psychological context of female sexuality

1.1 History

The field of sexual medicine has made remarkable progress both scientifically and clinically in the recent years. The development has been most apparent in the area of erection physiology, in which significant advances have been made with regard to understanding the mechanism of penile erection and developing effective therapy for erectile dysfunction. This model of success supported further efforts to promote the study of all sexual disorders in both men and women and advance their clinical management.

In their revolutionary work published in 1970, Human Sexual Inadequacy, Masters and Johnson were one of the first to systematically list various diagnoses of sexual dysfunction and included premature ejaculation, ejaculation incompetence, impotence, orgasmic dysfunction, vaginismus, and dyspareunia.[1] Desire disorders were not mentioned. The aetiology of sexual disorders was, until recent years, assumed to be primarily psychogenic thus a psychiatric nomenclature was originally developed to classify sexual disorders.

In the Diagnostic and Statistical Manual of Mental Disorders, Second Edition (DSM-II), desire disorders in either sex were not specifically diagnosed and all sexual disorders were grouped into one diagnostic category labelled psycho physiological genitourinary disorders.[2]

In 1977, two psychiatrists, Harold Lief and Helen Kaplan introduced the concept of low sexual desire.[3,4] A few years later, inhibited sexual desire was added to the official nomenclature in DSM-III (1980).[5] Since then, numerous smaller and bigger modifications have been made to the nosology alongside with the increase in understanding of both female and male sexual function. A final classification of sexual disorders has not been made mainly due to the lack of knowledge concerning the determinants of sexual function, - specifically sexual desire -, and the myriad of conditions that can influence libido.[6] Currently there are two primary diagnostic frameworks; the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual (DSM-IV-TR 2000), the major nomenclature of the latter (DSM-IV) being used in both psycho-therapeutic and pharmacological studies of treatment of Female Sexual Dysfunction (FSD). The primary characteristic in the DSM-IV category "sexual dysfunctions and disorders" is the impairment in normal sexual functioning. This can refer to an inability to perform or reach an orgasm, painful sexual intercourse, a strong repulsion of sexual activity, or an exaggerated sexual response cycle or sexual interest. A medical cause must be ruled out prior to making any sexual dysfunction diagnosis and the symptoms must hinder the person's everyday functioning. Hypoactive sexual desire disorder (HSDD) is one of the most prevalent sexual dysfunctions in women, especially after (surgical) menopause. HSDD is defined as persistent or recurrent deficient or absent sexual fantasies or desire for sexual activity in the presence of significant personal distress. Of note: in the absence of normative data, there are no specific behavioural referents for the diagnosis and there are no criteria that distinguish normal from abnormal levels of desire. The diagnosis whether a problem becomes a disorder is thus dependent on clinical judgement.

Historically, as HSDD was considered a psychiatric disorder, therapeutic approaches were based on education about sexuality, facilitation of sexual communication, psychoanalytic theory (Freud's "analysis of the resistance to the experience of sexual pleasure") and/or on social learning theories.
Since the mid-20th century, along with the scientific discovery of SSRI reuptake inhibitors which resulted in the emerge of the biological psychiatry, a group of clinicians and investigators began reporting evidence suggesting a possible relationship between endocrinological variables and libido in women.
This new research area, investigating biological causes for sexual dysfunctions, began around 1940, when incidental cases of increased libido where reported as a side affect of androgen therapy for treating certain cancers.[7,8]
Interestingly, Freud, who's idea's regarding psychotherapy have dominated the first half of the 20th century, was originally focussed on the biological causes of mental illness, including sexual disorders and spent many years in trying to understand personality through what we now call "neuro-endocrinology".

1.2 Models of the female sexual response

Masters & Johnson and Kaplan were the first to describe the female sexual response cycle starting with desire for sexual activity, followed by arousal, orgasm and finally resolution.[9] This traditional linear model (excitement, plateau, orgasm and resolution) implies that sexual thoughts and fantasies initiate arousal. (Figure 1)
Recently, Basson has proposed a new model for female sexuality, postulating that the linear sequence of mainly genital events may fit the male sexual response cycle but has not been proven helpful in understanding female sexuality.[10,11] In this model she states that spontaneous sexual desire might be absent in many women at the onset of a desired sexual experience and that emotional intimacy is the most important factor influencing a woman's initial responsivity. Women usually begin sexual experience in a neutral state. Arousal is triggered by deliberately sought sexual stimuli, including the behaviour between partners, conversation, music or physical stimulation. Once arousal is reached, it will foster sexual desire to continue the experience and finally result in emotional and physical satisfaction which increases the couple's intimacy. (Figure 2)
Like the Masters and Johnson model, this model is also conceptually grounded without being empirically tested in samples of women with and without sexual dysfunction. Recently, Sand and Fisher published a research in which a women's endorsement of brief descriptions of current models of female sexual function was investigated. It appeared that women in their study were equally likely to endorse each of the different models, emphasizing the heterogeneity of women's sexual response.[12]

Figure 1. Masters and Johnson's model of the human sexual response (Masters and Johnson, 1970)

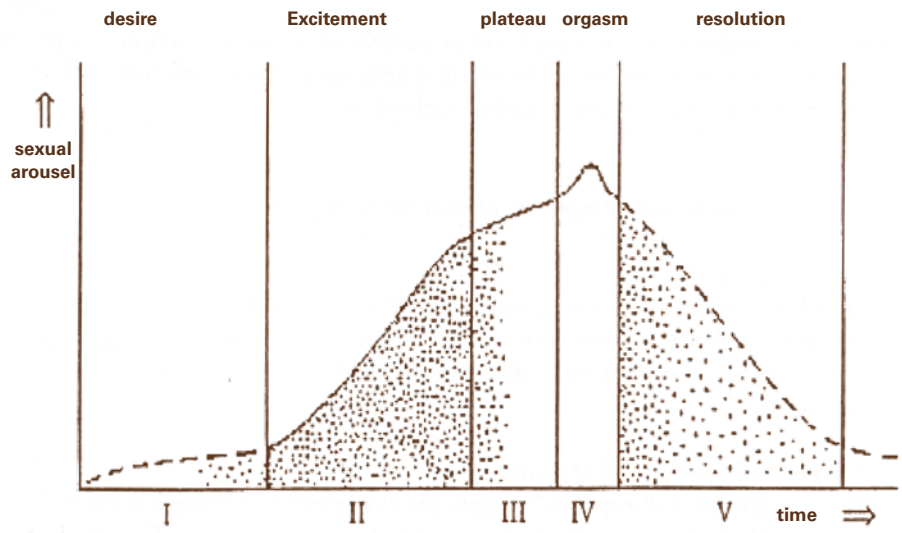
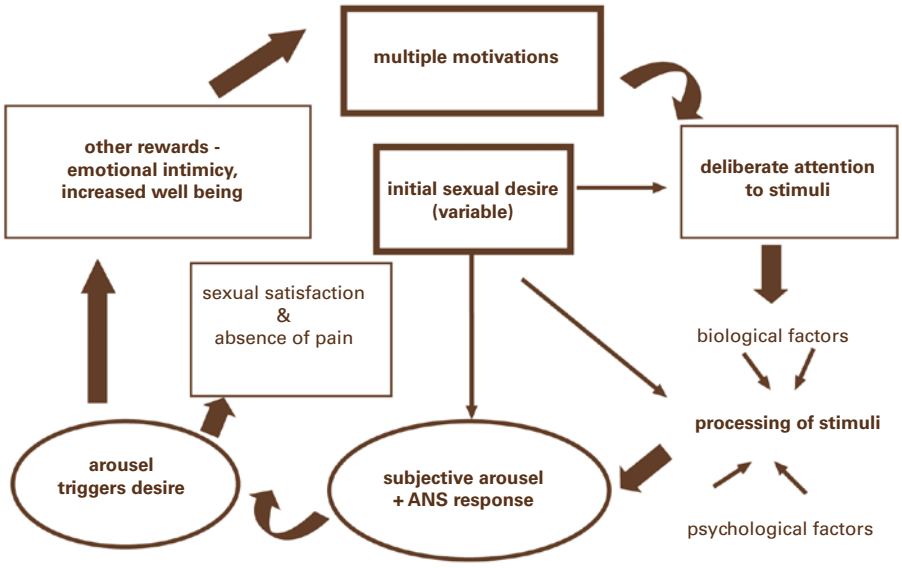


Figure 2. Basson's model of the female sexual response cycle. (Adapted from Basson, 2001)



1.3 Prevalence of female sexual dysfunction

Large scale population based studies in the US, Europe and globally suggest that between 25-43% of the women experience sexual problems.[13,14] Loss of sexual desire is the most common symptom of female sexual dysfunction with a prevalence reported in the literature between 30-40%.[13,15-17] Little data are available about the prevalence of sexual dysfunction meeting the criteria for diagnosis. The percentage of women with sexual problems represents an aggregate of all women reporting occasional, periodic or frequent sexual problems. Sexual problems of short duration may result from situational factors and can obviously not be counted as sexual disorders.[18] In addition, in most surveys the level of significant personal distress is not investigated, which is likely to be experienced by not more than 50% of the women reporting sexual problems.[16] The prevalence of HSDD (loss of sexual desire in the presence of significant personal distress) has recently been determined in two well designed population based studies: the prevalence was 14% in premenopausal women, 26% in young (20-49) surgically menopausal women, 9% in naturally menopausal women and 14% in older (50-70) surgically menopausal women.[16,19]

CHAPTER 2

Endocrinological context of female sexuality

2.1 Role of hormones in sexual function

The endogenous hormones that potentially influence female sexuality include oestrogens, androgens, progesterone, prolactin, oxytocin and glucocorticosteroids.
Although it is widely accepted that hormones exert an important influence on sexual functioning, it has been difficult to show correlations between endogenous sex-hormone levels and various aspects of sexuality. This might be partly due to the complex biomechanism(s) by which hormones operate which is not yet completely understood. Hormones interact with numerous neurochemicals within the central and peripheral nervous system, including serotonin, catecholamines, dopamine and other neurotransmitters and hormones. The factors that determine the outcome of the complex interaction depends on the absolute level of each hormone, their absolute receptor content, the presence and levels of specific co-activator and co-repressor proteins that modify the transcriptional response and the up or down regulation of receptor levels by other hormones.
Obviously, oestrogen and progestagen are of critical importance for sexual and reproductive function. Follicle maturation, ovulation and pregnancy maintenance depend on pituitary and gonadal hormones. Puberty, including its onset of conscious sexual feelings does not occur in the absence of the normal rise of these hormones. Oestrogen is thought to have no direct effect on sexual desire but it is important for the genital physiological response, whereas androgens are thought to play a role in motivational aspects of sexuality such as sexual desire and arousal.[20,21] Oestradiol levels have been reported to be a significant determinant of a woman's sexual function during the menopausal transition in addition to prior sexual function and relationship factors.[22] Androgens, produced by the ovaries and adrenal cortex, gradually decline with age with the steepest decline between the third and fifth decade and do not change with menopause and change very little with age in postmenopausal women.[23]
Some direct relation seems to exist between low oestradiol (below 50 pg/cm^3) and the presence of sexual complaints, although serum oestrogen levels do not reflect oestrogen action at the tissue level.[24,25]
There is no evidence that measurement of steroid hormones assist with the diagnosis of female sexual dysfunction (FSD), neither does a single androgen level predict low sexual function in women.[26,27]

2.2 Menopause and sexuality

Prevention suggests that the life expectancy for Caucasian women is now 80.5 years.[28] Therefore, the average woman may spend as many or more years in the postmenopausal phase of her life as she does in the fertile phase between menarche and menopause. Moreover, the widespread improvements in health care and lifestyle throughout the developed world have led to an increasing number of women to reach menopause in good physical and mental health. Surveys have shown that women expect to maintain a high level of health and quality of life during their postmenopausal years.

With menopause, and the decline in circulating oestrogens, the majority of women experiences changes in sexual function. Common sexual complaints include: loss of sexual desire and interest, decreased frequency of sexual activity, painful intercourse, diminished sexual responsiveness and a difficulties reaching orgasm.[29,30] The specific effects of menopause are confounded by the change in sexual function during normal ageing. However, the physical, emotional and psychological changes during the menopausal transition all influence aspects of a women's life including sexuality and are reported to be incremental and additional to those characteristic of ageing.[31,32] Sexual life in most women indirectly improves with oestrogen therapy: relief of a woman's vasomotor symptoms improves her quality of life, which can increase sexual interest. Only a few randomized controlled trials have been performed in which the effect of oestrogen on sexual function in postmenopausal women is investigated. Although these studies are dated small and did not include postmenopausal women identified with sexual dysfunction, there is support for a beneficial effect of oestrogen on sexual function.[33-37]

Many postmenopausal women continue to experience a diminished sexual interest and desire in spite of oestrogen treatment.[38] Exogenous testosterone supplementation has meanwhile proven to significantly improve sexual desire, arousal, responsiveness, orgasm, pleasure and satisfaction in both naturally and surgically postmenopausal women with HSDD.[39,40]

2.3 Effects of tibolone on sexual function

Tibolone, a selective tissue oestrogenic activity regulator, is metabolised in the gastrointestinal tract to the 3α and 3β metabolites, which then circulate predominantly in their sulphated inactive forms.[41] These metabolites become oestrogenically active when desulphated in target tissues such that tibolone is effective in the treatment of oestrogen deficiency symptoms. The global effect of tibolone would thus expected to be oestrogenic. Previous studies have suggested that tibolone may improve sexual function, particularly sexual desire and arousal, to a greater extent than traditional oestrogen-progestin therapy in healthy postmenopausal women.[42,43] These effects have been attributed to the intrinsic capacity of a tissue metabolite of tibolone, the Δ4-isomer, to activate the androgen receptor[44] and to the reduction in sex hormone binding globulin (SHBG) and hence the increase bio available testosterone.[45]

CHAPTER 3

Rationale for this thesis and research questions

The general and main research question was:

What are the effects of classical hormone therapy (oestrogen and progestagen) and specifically tibolone on sexual function in postmenopausal women with Female Sexual Dysfunction (FSD).

To address this general question several considerations were explored before identifying the approach to conduct this project as the female sexual response cycle is vulnerable and reflects an entity which is highly complex and dependent of many factors, hormones most likely being only a small part of the puzzle.
The aim of our study was to contribute to the current knowledge about the role of hormone therapy in female sexual function and to search for pharmacological treatment options which could fit in a multi-dimensional, but also clinically practical approach in the treatment of sexual problems.
In order to provide the necessary material for designing the FSD study and to answer our main research question, we defined sub-research questions as follows:

1. What are the attitudes of postmenopausal women and doctors regarding sexuality after menopause?
2. What is the correct research approach in investigating pharmacological intervention for FSD?
3. What are the effects of tibolone, combined oestrogen plus progestagen and raloxifene (a selective oestrogen receptor modulator) in sexual function in postmenopausal women?
4. What is the net androgenic effect of tibolone over and above its oestrogenic effects in postmenopausal women with FSD?

Outline

Chapter 4 identifies and describes current women's thoughts about sexuality after menopause in various European countries and identifies current physicians attitudes towards sexuality during and after the menopause.

Chapter 5 reviews the current knowledge about pharmaceutical intervention studies in FSD and addresses the limitations and issues in the study of FSD with regard to design and outcome measures.

Chapter 6 determines the effects of tibolone and raloxifene on health-related quality of life, sexual function and vaginal atrophy in elderly postmenopausal women.

Chapter 7 determines the effects of tibolone and low dose E_2/NETA on sexual function, urogenital complaints and quality of life in younger postmenopausal women.

Chapter 8 compares the efficacy on sexual function of tibolone versus continuous combined transdermal E_2/NETA in naturally postmenopausal women with sexual dysfunction.

Chapter 9 addresses tolerability issues of tibolone and transdermal E_2/NETA for treating FSD.

Chapter 10 aims to contribute to the current research area of FSD and presents explorative analyses of the pharmaceutical intervention study in women with FSD.

Chapter 11 presents the general discussion about the findings in our studies and integrates the results into clinical practice.

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PHARMACOLOGICAL INTERVENTION AND FEMALE SEXUAL FUNCTION AFTER MENOPAUSE

CHAPTER 4

Sexual Well-Being after 50:
A European Survey among Women and Physicians

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Submitted

Abstract

Objectives: To identify and describe current women's thoughts about sexuality after menopause in various European countries and to identify current physicians attitudes towards sexuality during and after the menopause.

Methods: 3182 postmenopausal women aged 50-60 years and 612 physicians were interviewed via a standardized interview in 6 European countries.

Results: 67% of all women reported to experience one or more symptoms affecting sexual well-being including vaginal pain/dryness, reduced sexual desire and/or sexual interest during or after menopause. Two third of the women reported that a reduced sexual desire influences quality of life and that it influences the relationship with the partner. The majority of women (61%) stated that sexual activity remains as important as before the menopause. The main reason for a reduced sex life (specifically lack of sexual interest and desire) reported by women is menopause and growing older whereas the physicians reported that the main reason is vaginal pain/dryness (80%) and/or menopause (57%). Most women with sexual problems never considered a treatment, however, if a treatment would be available, 35% was willing to try it to improve sexual functioning.

Conclusion: European middle aged women experience menopause as a process that brings sexual changes with impact on their relationship and their quality of life. Women and doctors see menopause related sexual problems differently: educating both women and doctors concerning sexuality may remain one of the crucial elements to resolve menopause related sexual problems.

Introduction

Previous surveys have shown that women expect to maintain a high level of health and quality of life during their postmenopausal years and most women consider sexuality to be an important component to perceived quality of life.[1-3] Sexual behaviour has generally been found to change with age[4-7] and menopause may have an impact on some aspects of sexuality such as sexual interest and desire 8 whereas satisfaction with the sexual relationship has not been found to correlate with either menopause or age.[9-11] In a prospective cohort study, women's sexual function was found to be more dependent of prior sexual function and relationship factors than of aging and hormonal factors.[12] Another important factor highly associated with distressing sexual dysfunctions in women is sexual dysfunction of the partner.[13]

Culture has been shown to impact sexual attitudes and sexual behaviour[14] and societal beliefs may play a role in the way women perceive sexual changes during ageing and as a result influence the way women answer sexuality questionnaires for diagnostic purposes. Two cross sectional studies have been performed on women's sexual functioning during midlife in various European countries[15,16] however, none of these studies has investigated a woman's opinion and perception of sexuality around the mid-age.

The prevalence and significance of sexual problems in women, including its medicalisation, have been an ongoing debate[17,18] and have underscored the need for additional research specifically focussed on a woman's opinion about her experiences related to sexual function.

The aim of the present study was to understand how postmenopausal women experience sexuality after menopause, their thoughts and attitudes about sexual well being in various European countries. The second aim was to identify the attitude of physicians towards sexuality after menopause and their behaviour towards sexuality-related menopausal symptoms of their patients.

Methods

This cross-sectional survey was conducted in February 2006 in six European countries (Belgium, France, Italy, United Kingdom, Sweden and Switzerland), including a stratified sample of 500 women, aged 50-60 years, per country. In France, the UK, Sweden en Switzerland the survey was conducted via a computer assisted web based approach. In Italy and Belgium women were interviewed via computer assisted personal interviewing (CAPI). In order to have results completely comparable with the on-line approach, the interviewers had to take place in another room or leave the house during the time the respondent filled in the questionnaire. The whole project was coordinated, by a professional independent market research organisation (TNS NIPO, Amsterdam, The Netherlands). Women in the survey had to be between 1-5 years past a natural menopause. Participation was voluntary, confidential and anonymous. The selection procedure was based on panel use and quotas where used for age, regional distribution and educational level to ascertain that the sample was representative of the overall

population of women from the six participating countries. Panels were drawn from databases which had been built during previous years as a result of Computer Assisted Telephone Interviewing (CATI). Where necessary (Belgium and Switzerland) the samples where boosted with additional external address files from address suppliers. The women were interviewed in their native language. The translations of questionnaires were prepared from the original English version by translators experienced in health and sexuality related surveys and then back-translated into the English version to validate the translation. The questionnaire itself was linguistically validated in a pilot study in 28 women in the UK.

In addition, approximately 100 doctors per participating country were aimed to be interviewed. The selection of doctors per country was dependent on whether they saw menopausal patients. In the UK general practitioners were interviewed and in the remaining countries the gynaecologists were interviewed.

The average duration of the interviews was approximately 15 minutes. The questions consisted of a combination of multiple choice questions (64 questions for women and 48 questions for doctors) and 4 open-ended questions for both groups. The questions in both questionnaires can be divided into the following categories:

- prevalence of menopausal symptoms and sexual problems
- defining sexuality
- importance of sexual activity and the impact of sexual problems on life quality
- willingness to discuss sexual well being and seek information about sexual problems
- attitudes about treatment for sexual problems

Women who reported to have experienced a reduced sexual interest or desire and/or vaginal pain/dryness as a problem since menopause were classified as "women with sexual problems" irrespective of the degree of personal distress. Women who did not report to have any of these problems were classified as "women without sexual problems".

Statistical analyses are descriptive. Calculations were carried out as exploratory analyses and all variables (including percentages) where compared using Chi-squared test, meaning that all results per group are compared with rest groups minus that one. All statistical tests comparisons with < 5% probability of error were considered to be statistically significant.

Results

The response rate varied from 65%-70% for the various countries 3182 postmenopausal women and 612 doctors equally divided over the countries were interviewed.

Prevalence of menopausal symptoms and sexual problems

Most women included in this survey experienced one or more postmenopausal symptoms which were comparable between countries in terms of frequency. The prevalence of individual symptoms reported by women and doctors is presented in Figure 1.

Two third (67%; n = 2132) of the interviewed women reported to experience one or more symptoms directly influencing sexual well-being such as vaginal dryness and reduced sexual desire and/or interest since their menopause. Vaginal pain/dryness/discomfort was mentioned by 34% of the women as being part of their menopausal problems whereas nearly twice as much (58%) of the doctors thought that this is one of the problems experienced by postmenopausal women. 54% of the women reported to have experienced reduced sexual interest and/or desire while only 32% of the doctors thought this is a problem experienced by menopausal women.

After hot flushes and sleeplessness, women ranked reduced sexual interest/desire and mood swings as third largest topic having an impact on their daily life. Vaginal dryness was not regarded as affecting much daily life contrary to the interviewed gynaecologists who ranked vaginal dryness higher than a reduced sexual interest/desire as an important factor influencing quality of life. See Figure 2.

Women in Italy and the UK ranked the influence on daily life of a reduced sexual interest and desire somewhat lower when compared to the other countries.

41% of the women with sexual problems reported to have a partner experiencing sexual problems (including a reduced sexual interest/desire) versus 17% of the women without sexual problems who reported to have a partner with sexual problems ($p < 0.05$).

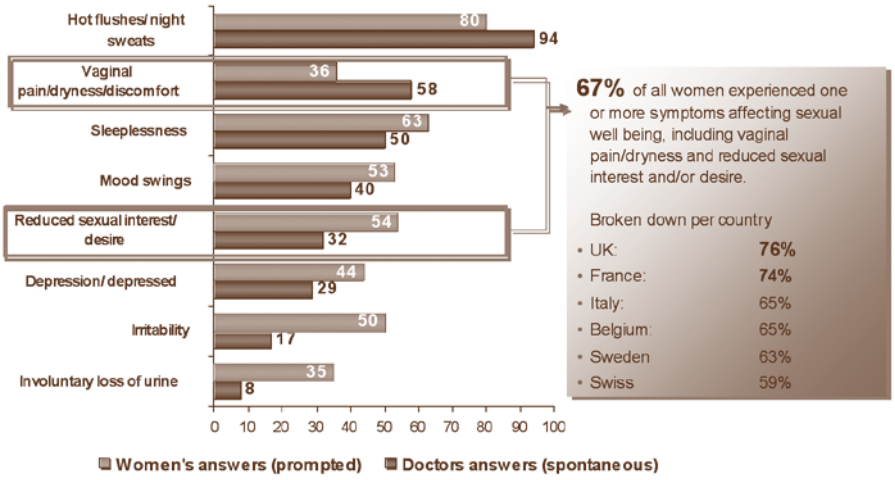
According to women, the main reason for a reduced sex life is menopause and growing older (57% and 54% respectively), followed by vaginal dryness and long-term relationship (31% and 29% respectively) and disease/illness and changed partners needs (19% and 21%). According to doctors the main reason for a reduced sex-life is vaginal pain/dryness (80%) and menopause and growing older (57% and 54%). See Figure 3.

Women were asked to estimate the percentage of postmenopausal women with low sexual desire and interest. Women without sexual problems estimated that this percentage was about 37%, women with sexual problems estimated 49% and doctors estimated that 55% of all postmenopausal women experienced a reduced sex drive.

Defining sexual activity and sexual activity frequency

In their own words, the majority of women described sexual functioning and sexual activity in terms of emotional closeness, intimacy, love and affection, mostly but not necessarily resulting in sexual intercourse. 40% of the women in France and 21% of the women in the UK were reluctant to answer the question: "how would you describe, in your own words sexual function and sexual activity" whereas for the other countries the

Figure 1. Menopausal symptoms according to women and doctors

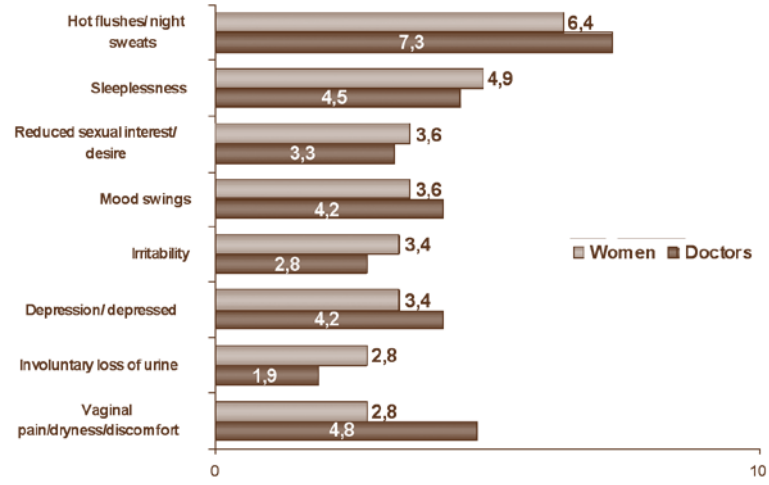


Q: Are you experiencing of have experienced any of the following symptoms in the past 5 years?/Wich symptoms indicate menopause (spontaneous)?

Base: All women who passed the screening/all doctors who see women wich menopausal symptoms

Sample size: n=2995/n=612

Figure 2. Symptoms with most influence on daily life, ranked in order



Q: Can you please rank the symptoms you mentioned according to how much they affect your life?

Base: All women that have one or more menopausal complaints and ranked their symptoms/doctors who ranked symptoms were 1 stands for no ranking and 9 for the highest ranking

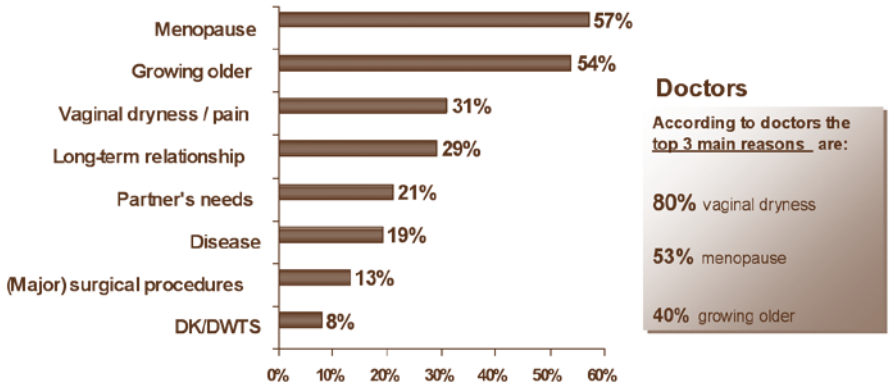
Sample size: n=2423/n=612

group of women having difficulties to answer this question ("don't know" or don't want to share) was around 10%.
Physicians described sexual functioning in more technical, physical terms such as ability to have intercourse, penetration, orgasm.
Before menopause, the initiative to sexual activity was taken by both partners equally in 55% of the surveyed women, 6% of the women reported to have taken the initiative mostly and in 37% the initiative was taken by the partner. After menopause 46% of the women with sexual problems reported that the initiative to sexual activity was taken by their partner only, versus 25% in the group of women without sexual problems ($p < 0.001$). The Italian women scored highest both before and after menopause in the percentage of their partners taking the initiative to sexual activity (54% and 58% respectively versus the lowest percentage in the UK 25% and 37% respectively before and after menopause).
The majority of women reported that their level of sexual activity has dropped since entering the menopause. Nevertheless, the majority of women in each of the two groups, -women without sexual problems and women with sexual problems-, reported to have a sexual activity frequency of twice or more per month (74% and 56% respectively for women without and with sexual problems, $p < 0.001$). In both groups, the percentage of women not having had sex in the past 3 months was 15%.
In the group of women without sexual problems the percentage of women reporting to have a sexual activity frequency of 2 or more per month is highest in Sweden (73%). However, the percentage of Swedish women with sexual problems reporting to have a sexual activity frequency of ≥ 2 per month is one of the lowest when compared to the other countries (46%). The percentage of French and Swiss women reporting a sexual activity frequency of ≥ 2 per month in spite of a reduced sexual interest/desire is relatively maintained when compared to the women without sexual problems in their countries (French women with sexual problems: 60% and Swiss women with sexual problems: 61% respectively versus 66% and 72% of the French and Swiss women without sexual problems).

Importance of sexuality and impact on quality of life

85 % of all women reported that it is very important to maintain an intimate relationship after menopause and also the majority of all women (61%) stated that sexual activity is as important or more important as before menopause. However, 21% of this group found sexual activity less satisfying when compared to pre-menopause. Aspects such as intimacy with the partner, sexual pleasure, love, orgasm, feeling attractive/feminine, happiness and getting attention were all important aspects of sexual activity to the majority of women both before and after menopause. However, a reduction of these aspects is experienced after menopause by most of the women. Differences existed at a country level, for instance women in the UK tended to expect much more emotional benefit from sexual activity than women in Italy specifically when it concerned aspects like feeling feminine (UK 62%, Italy 36%), feeling attractive (UK 68%, Italy 34%), happiness (UK 66%, Italy 23%), attention (UK 56%, Italy 22%), respect (UK 51%, Italy 20%) and women with sexual problems reported less importance of the above aspects (emotional benefits) from sexual activity than women without sexual problems.

Figure 3. The main reasons for reduced sex drive according to women



Q: Reduced sexual function does not usually exist independently, but as a consequence of various factors. What do you consider to be the main reason for your reduced sex drive?

Base: All women who passed the screening and have (ever) experienced a reduced sex drive and all doctors

Sample size: n=1917/n=612

77% of the women agreed with the statement that sex is an important aspect of their relationship and 74% of this group was satisfied with their current sexual relationship.

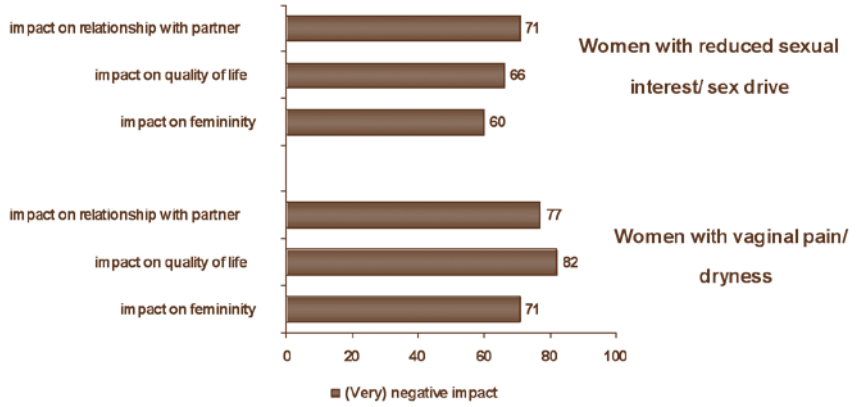
74% of the women without sexual problems (n = 1032) reported to experience pleasure from sexual activity more than half of the time versus 44% of the women with sexual problems ($p < 0.001$). 39% of the women with sexual problems experienced pleasure from sexual activities less than half of the time versus 9% of the women without sexual problems ($p < 0.001$).

A reduced sexual desire was reported by 71% of the women to influence the relationship with the partner; 66% reported that it has an influence on quality of life and 60% reported that it has an impact on femininity. A similar percentage of women reported to experience an impact from vaginal dryness/pain on the relationship with the partner (77%), quality of life (82%) and femininity (71%).

Doctors reported higher frequencies of the impact of vaginal dryness and reduced sexual desire on their patients life. Figure 4a and 4b.

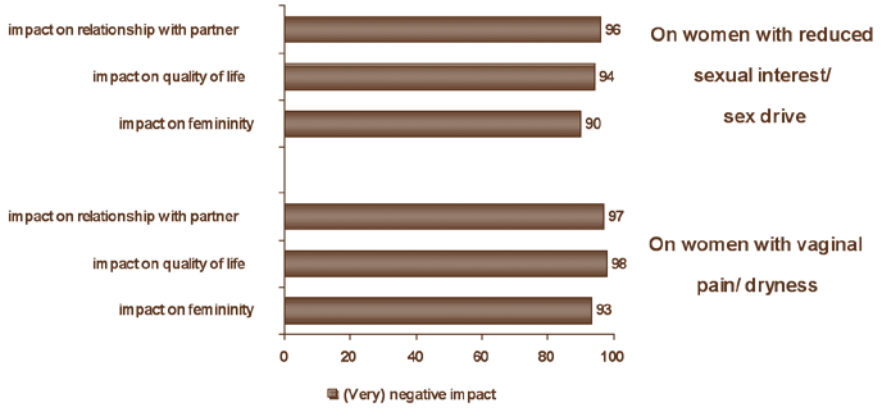
Statements about reduced sexual function such as "loss of sexual function (would) make(s) me unhappy", "a reduced sexual function (would) make(s) me less feminine", "loss of sex drive (would) negatively influence(s) my quality of life", "a reduced sexual function (would) give(s) me less confidence/self esteem", were confirmed by approximately half of the women equally divided over the women reporting with sexual and without sexual problems. Physicians had a much higher confirmation rate of these statements (approximately 75%; $p < 0.001$). See figure 5a and 5b. The percentage of women

Figure 4A. Impact of reduced sexual interest/sex drive and vaginal pain/dryness (**women**)



Q: To what extent does reduced sexual interest or vaginal pain have an impact on your quality of life/feminity/relationship with partner, **Base:** All women who have experienced a reduced sexual interest (sex drive) and vaginal pain, **Sample size:** n=1608

Figure 4B. Impact of reduced sexual interest/sex drive and vaginal pain/dryness (**doctors**)



Q: To what does a reduced sexual interest of vaginal pain have an impact on a womam's quality of life/femininity/relationship with partner, **Base:** All doctors who consider reduced sexual interest of vaginal pain menopause related, **Sample size:** n=508/n=583

in France, Italy and the UK agreeing with these statements was relatively higher than in Sweden and Switzerland ($p < 0.05$).

The majority of women could openly discuss their sexual needs and desires with their partner, however, the group of women who could not discuss sexual issues with their partner was twice as high in the group with sexual problems when compared to the women without sexual problems (21% versus 11%).

Willingness to discuss sexuality

For 30% of the women, discussing sexual problems is a taboo whereas also 37% of the doctors agreed with this statement. The Italian, French and UK women were most reluctant to talk about sexual problems (35%, 38% and 33% respectively) whereas the Swiss doctors are (46%). Talking about sexual problems is regarded by 32% of the doctors to be more difficult with elderly women than with younger women. 7 out of 10 women would discuss their sexual problem if their doctor would bring up the subject, however, 31% of the doctors would always wait till the patient brings up the subject. There is no difference between male and female doctors with regard to the having the feeling that they could openly discuss sexual topics with most of their patients. 62% of the physicians has actively searched for information concerning menopause related sexual problems, whereas only 17% of the women did. Main information sources for women were: women's magazines, gynaecologists, books, friends/internet and the most important source of information was regarded to be the gynaecologist. The most useful information for women was: "the feeling not to be alone in this", "possible treatment information" and "talking to the physician". Half of the women who had searched for information found that they had not found any useful information at all.

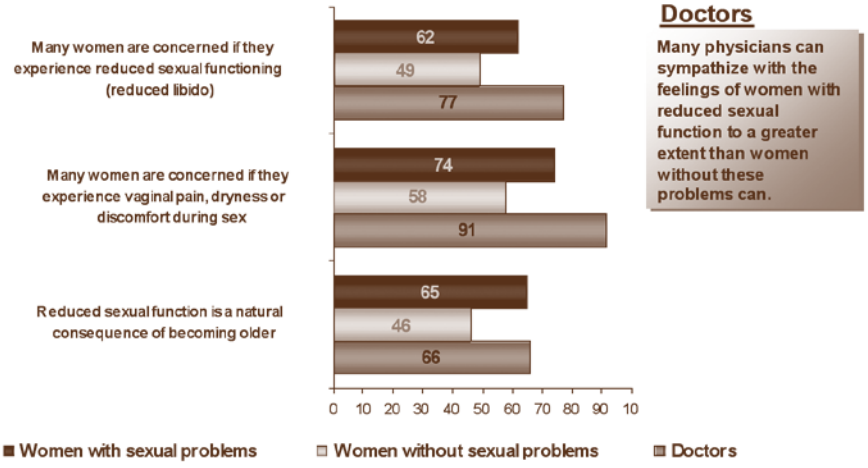
Attitudes about treatments for sexual problems

39% of all women had ever used or been prescribed hormone treatment (HT) for climacteric symptom relief (highest: UK (53%) and lowest: Italy (19%). 27 % of the women had used or been prescribed natural/herbal treatments and 36% had not used any treatment ever. Women with sexual problems had a higher usage of various treatments (including HT and natural remedies) for menopausal symptoms than women without sexual problems (68% vs. 56%; $p < 0.05$).

Most women with sexual problems have never considered a treatment (78%, n = 675 sample base: all women with reported reduced sexual function who have never used any treatment), as the majority (67%) was not bothered enough and could live with it. 23% did not find a reduced sexual activity that important and 20% thought that it is an evitable part of going through menopause. In an open ended question to doctors which treatments they were aware of for sexual problems the majority answered HRT (80%). Other treatment options doctors were aware of were counselling (30%), vaginal lubricants (22%), testosterone (20%).

40% of the doctors sometimes prescribed a treatment for sexual problems whereas another 40% reported to do this frequently. Among a variety of advices doctors gave, such as explaining the problem, reassurance, life style changes, lubricants, topical

Figure 5A. Statements reduced sexual function and sex drive analyzed by level of agreement (**women**)

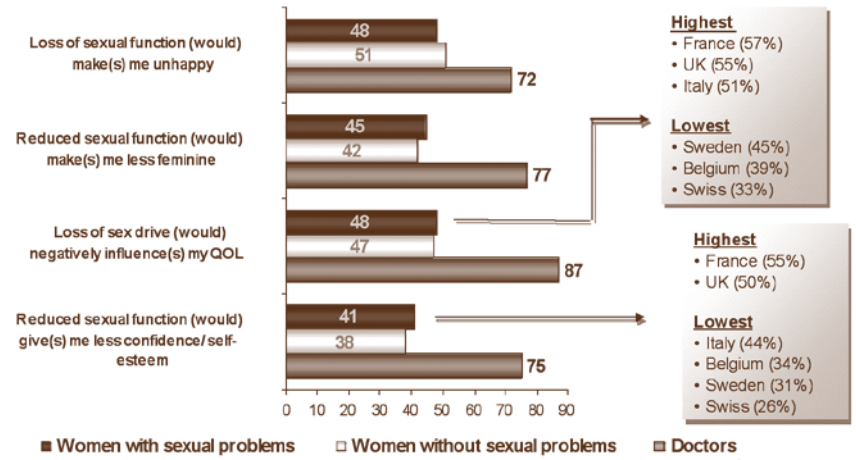


Q: Statement about reduced sexual function

Base: All women who passed the screening, analyzed by sexual problems and all doctors

Sample size: n=3182 (of wich n=2139 have sexual problems, n=1043 do not have sexual problems)/n=612

Figure 5B. Statements about reduced sexual function and sex analyzed by level of agreement

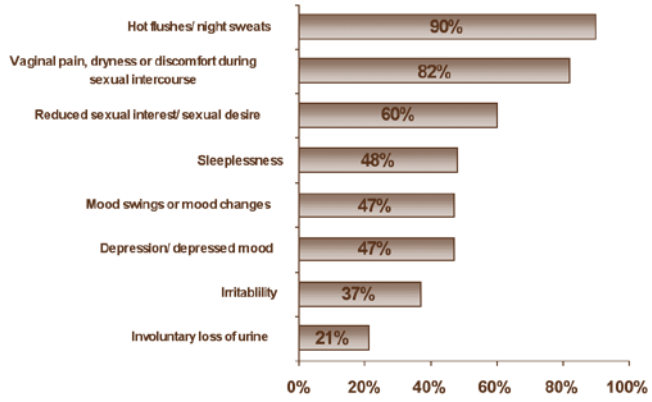


Q: Statement about reduced sexual function and sex drive by level of agreement

Base: All women who passed the screening analyzed by sexual problems and all doctors

Sample size: n=3182 (of wich n=2139 have sexual problems, n=1043 do not have sexual problems)/n=612

Figure 6. Initial reasons for doctors for offering HRT as treatment for reduced sex drive



Q: You have mentioned that you prescribe(d) Hormone Replacement Therapy (HRT) as treatment for women with a reduced sexual function. What were the initial main reasons to offer this treatment (prompted answers)?
Base: All dotors who prescribe natural or herbal homeopathic treatments
Sample size: n=574

estrogens, 29% of the doctors initially advised HRT as a treatment and 17% advised women to discuss their sexual problems with their partner.
The initial reasons for doctors to offer HRT as a treatment for a reduced sex drive were mostly vasomotor symptoms (90%), vaginal dryness/dyspareunia/painful intercourse (82%). However, 60% offered HRT initially for a reduced sexual interest/desire. See Figure 6.
76% of the doctors found HRT effective for the treatment of sexual problems. One third of the doctors prescribed herbal/natural treatments for the treatment of menopause related sexual problems (for which the initial reason to prescribe was also vasomotor symptoms). Also a few doctors (n = 57) prescribed anti-depressants as a therapy initially for sexual problems.
Most women were not aware of any effective treatment to help solving sexual problems (57%) and 28% thought that there is none. 62% of the doctors had no confidence in medication to solve sexual problems. If a treatment was available for reduced sexual desire, 38% of the women would be willing to seek treatment to help solving sexual problems and 35% would be willing to take medication to improve sexual functioning. 81% of the physicians would be willing to refer a patient to a sex-therapist and 55% of the physicians are open to learn more about sexuality related treatment and nearly all physicians would be interested in explaining more to patients about an effective treatment for loss of sex drive if this was available.

Discussion

The present survey shows that many women (67%) experience one or more problems influencing sexual well-being after menopause. In addition, all emotional benefits women mention to experience from sexuality, such as intimacy with the partner, love, physical pleasure and self-esteem, decreased after menopause. Women themselves give various reasons for the reduction in sexual function varying from ageing, menopause, long term relationship to medical conditions (illnesses) and changes in partner's sexual needs. To the majority of women sexual activity is a critical part of a good relationship and an important factor affecting quality of life. In spite of a high prevalence of sexual problems, many women remain sexually active, however, women with sexual problems obviously experience less pleasure from sex. Differences at a country level exist; French and Swiss women maintain their level of sexual activity frequency to a higher extent when experiencing sexual problems when compared to women in Sweden and the UK. In spite of 54% of all women reporting to experience a reduced sexual desire/interest, the majority of women (75%) is satisfied with their current sexual relationship. Only one third of the women reports to experience vaginal symptoms such as vaginal dryness, discomfort, dyspareunia and this is not ranked as one of the major symptoms influencing quality of life. The percentage of doctors being of the opinion that vaginal dryness is one of the major sexuality related symptoms is much higher and doctors rank vaginal dryness/painful intercourse as one of the most uncomfortable menopausal symptoms affecting quality of life as well as being one of the major reasons for a reduced sex drive after menopause.

It is interesting that the physicians interviewed in this survey overestimate the incidence and importance of vaginal dryness as recently it has been reported that, although urogenital ageing results in changes in the anatomy and physiology of the genitals, postmenopausal women preserve their genital responsivity when sufficiently sexually stimulated.[19] However, elderly women need more direct and longer stimuli as ageing affects peripheral response. In this context it is important to know the partners sexual interest as many women with sexual problems in this survey often have a partner with sexual problems, which is one of the major influencing factors on female sexuality.[20]

After menopause, women with sexual problems loose the initiative to sexual activity when compared to women without sexual problems. Differences exist at a country level. For instance the Italian women do expect less from sexual activity before and after menopause than the women in the UK with regard to feelings of pleasure/love/self esteem.

Our survey confirms that women have various reasons to be involved in sexual activity and a reduced sexual desire is not a measure for sexual dysfunction.[21] For instance in Italy it is much more common that the male partner takes the initiative to sexual activity and most Italian women continue to have sexual activity in spite of a reduced sexual desire. The prevalence of reduced sexual desire in postmenopausal women was somewhat overestimated both by women and doctors. In a recent publication about the true prevalence of Hypoactive Sexual Desire Disorder (HSDD), the prevalence of low sexual desire in naturally postmenopausal women was 29% and in combination with

significant personal distress, the prevalence was only 9%, a percentage which is markedly less than previous, less well designed surveys.[16,22]

One third of the women, specifically in the UK, Italy and France, are reluctant to discuss their sexual problems as well as 37% of the doctors but 7 out of 10 women would discuss their problem if their doctors would bring up the subject.

Most women would not consider any treatment for their sexual problems as they are not bothered enough by it. This underscores that women who do deliberately seek a doctor for their sexual problems merit therapy especially when there is sexuality related personal distress.[23] Most doctors offer HRT (oestrogen plus progestagen combinations) as a treatment if this is required. According to the literature, major influencers on post-menopausal sexual function are circulating E_2 levels and the severity of climacteric symptoms.[24] As a consequence, and confirmed in this survey, the majority of the doctors finds HRT effective for the treatment of sexual problems.

Strengths of this survey are that a randomized sample technique is used and not a convenience sample such as a clinic sample and that both women and doctors are interviewed with similar questions in order to gain information about the discrepancies in perception of sexual problems. The sample size per country was large enough to assess country differences. Furthermore, this is the first survey in which a woman's attitude and perception about sexual function is questioned in order to get an insight how important sexual problems really are after menopause.

Weaknesses of this survey are that it is a cross sectional survey and not a prospective cohort. Any perception of current sexual function is therefore biased by recall bias. Another weakness is that we did not use validated questionnaires, including a personal distress scale, to be able to make a balanced distinction between women with and without sexual problems or sexual dysfunction in this survey. The response rates were high but mostly samples were used of women and doctors who had previously participated in surveys or had expressed a willingness to do so, which might limit the generalizability of the findings.

Recently a proposal for changes in diagnostic criteria for changes in sexual dysfunction has been made in which the suggestion is made to clearly distinguish sexual disorders from transient alterations in sexual function related to life stress and relationship problems.[25] It might be useful to put women's sexual problems in a cultural perspective as well. Recently, a large scale multi-country survey investigating sexual attitudes and behaviours has been published in which was shown that sexual attitude and behaviour is influenced by effects which can be unique for a certain region in the world. In addition, the likelihood of sexual problems among women was not found to increase with ageing whereas it was for men's sexual problems.[26] It is likely that cultural forces and the perception of the female role across the countries may be major determinants of the sexual experience after menopause. Educating may play a crucial role in women's perceived sexual problems especially since this survey shows as well that women gained much information from women's magazines but that the information received by a physician is regarded much more useful. Important aspects included the knowledge that changes in sexuality are common over life time and just discussing this with a professional. In this respect it is important to stress that most women would bring up

the subject of sexual problems if their doctor would ask for it and in many cases discussing the subject would already be a part of the therapy.[27]

Conclusion

These data suggest that European middle aged women experience menopause as a process that brings sexual changes able to impair their personal life. However, cultural values and health beliefs influence the perception of sexual changes and the need for treatment. Women and doctors see menopause related sexual problems differently. Educating both women and doctors concerning sexuality may remain one of the crucial elements to resolve menopause related sexual problems.

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CHAPTER 5

Female Sexual Satisfaction and Pharmaceutical Intervention: a Critical Review of the Drug Intervention Studies in Female Sexual Dysfunction

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Abstract

Introduction: A considerable number of double-blind randomized controlled studies investigating the effects of pharmaceutical intervention on female sexual functioning have been published in the recent years. However, a comparison between outcomes of various studies is difficult as no general accepted/correct approach to research has been established yet. To be able to translate trial results to daily clinical practice, current limitations and issues in drug intervention studies in Female Sexual Dysfunction need to be clarified.

Aim: To evaluate the needs in research into intervention in female sexual dysfunction (FSD) by reviewing published studies.

Methods: A systematic review of double blind randomized controlled intervention trials on FSD.

Main Outcome Measures: Definitions of study populations, inclusion and exclusion criteria, use of power calculations, outcome measures and treatment duration.

Results: 25 double-blind randomized controlled trials investigating the effects of pharmaceutical intervention on female sexual functioning have been published. Of these, 11 studies required the diagnosis of FSD as an inclusion criterion. A standard methodology for research in this field is lacking. Significant differences in population inclusion requirements and tools for the measurement of change in sexual functioning were identified as major limiting factors.

Conclusions: The investigation of FSD is an evolving area in that new definitions and a new model for female sexual functioning have been recently proposed. There is a need for experts in the field and regulating authorities to reach a consensus regarding appropriate inclusion and exclusion criteria for FSD trials and main outcome measures appropriate for the evaluation of drug interventions. This consensus should also determine which treatment effect is considered to be clinically relevant. Treatment efficacy and clinical relevance should be related to outcomes which are meaningful for affected women.

Introduction

The study of FSD - an evolving area of research

In recent years the study of Female Sexual Dysfunction (FSD) has received increasing attention. However, understanding of factors relevant to research into female sexual functioning has lagged behind research into male sexual health.

In contrast to research in male sexual function, no gold standard self assessment instrument exists for research into female sexual function. Major reasons for the lack of standardized instruments are uncertainty as to the definition of 'normal sexual function' and the continuous evolution of the definition of FSD.

Normative data of sexual behavior across the adult female life-span is lacking. This contributes to difficulty in classifying a sexual problem as a sexual dysfunction. In the literature, much reference is made to a few population based studies which have indicated that the prevalence of sexual problems among women ranges from 9-43%.[1-4] However, the validity and reliability of these data is uncertain as epidemiological studies on female sexual function are constrained by the limited response rate, the limited use of validated instruments including addressing sexuality related personal distress and lack of information about the duration of sexual problems and the context of sexual problems.[5]

The second reason for the lack of one or two generally accepted standardized questionnaires for research into FSD is that the classification system for sexual disorders according to the DSM-IV-R classification system has been revised repeatedly resulting in new definitions for FSD by subspecialty groups (American Foundation for Urologic Disease, AFUD classification 2000 and revision 2003).[6-8] The proposed reclassification is based on a non-linear model of women's sexual response that explicitly recognizes its contextual nature, the variable sequence of desire and arousal and the frequent lack of correlation between subjective and physical (genital) arousal. Subsequently, the criteria for performing intervention trials in FSD have been proposed by individual expert groups and authorities.[9,10] However, no standardized approach to research has been established or meaningful endpoints agreed upon.

The Food and Drug Administration's (FDA) 2000 draft guidance document for FSD clinical trials recommends the use of the change in the frequency of successful satisfactory sexual events recorded in a daily diary as the primary endpoint and self administered questionnaires (SAQ's) as secondary endpoints.[9] The applicability of this approach has been criticized by a number of experts in the field.[11]

The complexity of the female sexual response and the strong impact of contextual factors, make the definition of endpoints and outcomes challenging. It has been proposed that the best predictors for changes in sexual response are contextual factors including previous sexual function, change of partner or feelings for partner.[12] Sexual behavior is ultimately, social behavior ("it takes two to tango") and where a loss of certain aspects of sexuality like arousal or interest does not automatically result in sexual problems or sexual dysfunction, an increase in sexual arousal or interest does not automatically result in sexual happiness and satisfaction.

Issues in FSD research that deserve consideration include selection of study populations and study design.

Aim: to summarize the current limitations and issues in randomized controlled trials in FSD with regard to design and outcome measures. We have not reviewed the efficacy of the various pharmaceutical preparations on FSD. The relevance of the outcomes of studies in FSD with regard to clinical practice is reviewed, unresolved questions identified and proposals to optimize the design of future studies made.

Methods

We included pharmaceutical intervention studies in healthy women identified as having FSD. FSD was defined according to the revised DSM-IV definitions or AFUD classification and included hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), female orgasmic disorder (FOD) and sexual pain disorders or a subgroup or combination of these.[5,6,13] A literature search for relevant studies was performed using PubMed from 1980-2005 (key words: female sexual dysfunction, menopause, hormones, estrogens, testosterone, sildenafil, DHEAS, androgens). Reference lists from the retrieved articles were also examined.

Only the following studies were included for this review: double-blind randomized controlled trials of women identified with FSD based on specific questions and/or an interview by an expert in sexuality. The studies were required to have included specific and comprehensive measures of sexual function.

We excluded studies in surgically menopausal women being "assumed to have FSD" as a result of the rapid and sudden decline in sex-steroids after oophorectomy as ovariectomy does not necessarily result in FSD.[14-16]

We defined the outcomes of interest as definition of the study population, inclusion and exclusion criteria, use of a power calculation, outcome measures used (questionnaires and hormone measurements) and treatment duration.

Results

A total of 25 double blind randomized controlled trials investigating the effects of pharmaceutical intervention on female sexual functioning have been published.[14,17-40] Of these, 11 studies were considered to meet the criteria for inclusion in this review and are listed in Table 1.

Four studies investigated the effects of sildenafil on sexual arousal disorder or combined sexual arousal and desire disorders[28-31] and seven studies investigated the effects of various testosterone preparations on sexual desire disorder and/or "low libido".[32-38] A recent study of Davis et.al was not included in spite of meeting the selection criteria for this review as this study was a rather mechanistic study investigating the effects of aromatase inhibition on testosterone treatment effects on FSD.[40]

Defining the target population

As recognized screening tools do not exist for FSD, the trial populations for the included studies were defined by non-standardized methods resulting in heterogeneity of the populations studied, with possible effects on trial outcomes.

Shifren et.al. included surgically menopausal women with "impaired sexual function" based on 3 qualitative questions.[32] All questions if answered affirmatively could indicate FSD, but these questions were not diagnostic for FSD. To overcome this problem, women also completed the Brief Index of Sexual Functioning for women (BISF)[41] and were included for participation only if their composite score was less than 33.6, which is the mean value for normal women. As there is a broad normative range of sexual functioning, a composite score below the mean score for normal women does not confirm FSD.

Some but not all of the subsequent studies included, in addition to a non-standardized interview, a variety of questionnaires assessing the degree of sexual function/dysfunction and the degree of sexuality related personal distress. Warnock et.al. defined the study population by a score below 8 on the Sexual Desire/Interest subscale of the Changes in Sexual Functioning Questionnaire (CFSQ-F-C)[35,42] and Goldstat et.al. included only women with diminished sexuality according to the Sabbatsberg Self-rating Scale (score $\leq$ 42).[34, 43]

In the testosterone patch studies, surgically menopausal women with hypoactive sexual desire disorder (HSDD) were included.[36-38] Women were identified if they had experienced a meaningful loss of sexual desire, a decrease in sexual activity after surgery and being bothered/concerned by this decrease in sexual desire.

Basson et. al. aimed to include women specifically identified with genital sexual arousal disorder based on a semi-structured interview.[30]

None of the studies defined their populations by the amount of sexuality related personal distress.

Only four studies included sexuality-related personal distress as and outcome measurement: Basson et.al[30] used a 4 point scale, rating from satisfied to distressed, to measure the level of personal distress with orgasm. In the studies of Buster, Simon, Braunstein[36-38] the Personal Distress Scale (PDS-7 items)was used as an outcome measurement.[44]

Inclusion and exclusion criteria

Inclusion criteria of the trials listed in table 1 were dependent upon the defined target population, that is, the specific sexual disorder (FSAD, HSDD, or "broad spectrum FSD") under investigation.

Age and menopause status:

Four trials[31,36-38] included women with considerably wide age limits ranging from 24 to over 70 and two trials have included women with both natural and surgical menopause.[31,33]

Basson et.al. included a combined population of premenopausal and postmenopausal women.[29] The results were reported separately for estrogenized (pre-and postmenopausal women, age 18-58) and estrogen deficient (non HT suppleted) women.

Table 1. Randomized controlled intervention trials in FSD

Author	Study	Treatment Time	N	Dose	Participants
Caruso et.al. 2001[25]	RCT placebo cross-over vs.sildenafil	Three 4- week periods	53	Sildenafil 25 mg and 50 mg	Fertile women 22-28 years
Basson et.al 2002[29]	RCT double blind placebo vs. sildenafil	12 weeks after a 4-week run in	781	Sildenafil 10 mg, 50 mg, 100 mg	577 estrogenized women (pre-and postmenopausal) age 18-55 and 204 estrogen deficient women age 45-70 years
Basson et.al. 2003[30]	RCT double blind placebo cross over vs. sildenafil	1 hour prior to vibro and audiovisual erotic stimulation	34	Sildenafil 50 mg	Postmenopausal estrogenized women 40-78 years
Berman et.al. 2003[31]	RCT double blind placebo vs sildenafil	12 weeks after a 4-week run-in period	202	Sildenafil 50 mg	Postmenopausal women 30-74 years
Shifren et.al. 2000[32]	RCT double blind placebo vs testo-sterone	12 weeks after a 4 week run in period	75	Testosterone matrix patch 150 µg or 300 µg daily	Estrogenized surgi-cally postmenopausal women 31-56 years
Lobo et.al. 2003[33]	RCT double blind placebo vs methyl-testosterone	16 weeks after a 2-week run in period	218	Methyltestosterone 1.25 mg p.o. daily	Estrogenized post-menopausal women 40-65 years
Goldstat et.al. 2003[34]	RCT double blind placebo cross over vs testosterone	12 weeks+ 12 weeks	49	Testosterone 1% cream 10 mg daily	Premenopausal women 30-45 years
Warnock et.al 2005[35]	RCT double blind placebo vs methyl-testosterone	8 weeks	102	Methyltestosterone 2.5 mg p.o daily	Estrogenized surgi-cally postmenopausal women 33-62 years
Buster et.al. 2005 (Intimate SM2 study)[36]	RCT double blind placebo vs testo-sterone	24 weeks after a 8 week run in period	533	Testosterone matrix patch 300 µg twice weekly	Estrogenized surgi-cally postmenopausal women 20-65 years
Braunstein et.al. 2005[37]	RCT double blind placebo vs testo-sterone	24 weeks	447	Testosterone matrix patch 150, 300 and 450 µg twice weekly	Estrogenized surgi-cally postmenopausal women 24-70 years
Simon et.al. 2005 (Intimate SM1 study)[38]	RCT double blind placebo vs testo-sterone	24 weeks after a 8 week run in period	562	Testosterone 300 µg twice weekly	Estrogenized surgi-cally postmenopausal women 26-70 years

FSAD: Female Sexual Arousal Disorder, HSDD: Hypoactive Sexual Desire Disorder, FOD: Female Orgasm Disorder, VPA: Vaginal Pulse Amplitude, PEQs: Personal Experience Questionnaire, GEQ: Global Efficacy Questions ("Did treatment improve physical response during sexual activity?" and "Did treatment improve ability to participate in sexual intercourse?"), LSC: Life Satisfaction Questionnaire, DSFI: Derogatis Sexual Functioning Inventory,

Inclusion	Outcome Measures	Sexual behaviour	Adequate Power
FSAD	PEQS Quality of Life by a 5-point Likert scale	↑arousal, orgasm, emjoyment, frequency of sexual fantasies and intercourse	No
Lubrication problems, FSAD, HSDD, FOD or combinations Score ≥5 on LSC (i.e. satisfactory sex life)	2 Global Efficacy Questions LSC SFQ	No change in sexual response	Yes
FSAD and impaired orgasm Various levels of disstress by orgasmic functioning (rating from satisfied to distressed)	Orgasm latency time Orgasm intensity DSFI VPA Beck anxiety inventory	No effect on orgasm latency and intensity. No change in subjective sexual arousal or genital arousal. Low VPA predictive for orgasmic response on treatment	No
Primary diagnosis FSAD, secondary HSDD allowed Minimal serum levels of estrogen and testosterone required (no estrogen and/or androgen insufficiency	FIEI SFQ Sexual event logs	In women without concommitant HSDD: ↑genital sensation during intercourse/stimulation. ↑satisfaction with intercourse and/or foreplay. No change in number of satisfying sexual events	Yes
Impaired sexual function after hysterecotmy/oophorectomy	BISF-W Daily diary (fantasies, desires and sexual activity) Serum hormone concentrations	↑subscores and mean of total score BISF (post hoc: only significant for women< 48 yrs). Overall big placebo response. No change in sexual activity according to the daily diary	No
HSDD with the onset of menopause. Score ≤ 3 on the thoughts/ desire dimension BISF. Deficit of ≥2 points from premeno-pausal level of desire on SIQ	MSIQ BISF-W Serum hormone concerntrations	↑ sexual interest/desire subscore SIQ No improvement in BISF (p=0.057)	No
Low libido (SSSR scale score < 42), BDI-I score < 28 (no depression), early morning testosterone serum level < 2.2nmol/L	SSSR Scale PGWBI BDI Serum hormone concentrations	↑in composite scores PGWBI and SSSR	No
HSDD with the onset of menopause. Score ≤ 8 on sexual desire /interest dimension of the CSFQ-F-C and a SES score ≤ 3	CSFQ-F-C CSES MSIQ WHQ Serum hormone concentrations	No change in CSFQ-F-C scores ↑subscore MSIQ (sexual desire/interest)	No
HSDD with the onset of surgical menopause	SAL PFSF PDS Serum hormone concentrations	↑satisfying sexual activity ↑sexual desire ↓personal distress	Yes
HSDD with the onset of surgical menopause menopauseBDI-II score ≥ 14 (no depression)	SAL PSFS PDS Serum hormone concentrations	↑satisfying sexual activity ↑sexual desire ↓personal distress	Yes
HSDD with the onset of surgical menopause. BDI-II score ≥ 14 (no depression)	SAL PSFS PDS Serum hormone concentrations	↑satisfying sexual activity ↑sexual desire ↓personal distress	Yes

SFQ: Sexual Function Questionnaire , FIEI: Female Intervention Efficacy index, BISF-W: Brief Index Sexual Functioning-Women, MSIQ: Sexual Interest Questionnaire , SSSR: Sabbatsberg Sexual Self Rating scale, PGWBI: Psychological General Well-Being Index, BDI: Beck Depression Inventory, CSFQ-F-C: Changes in Sexual Functioning Questionnaire-Female, CSES: Changes Sexual Energy Scale , WHQ: Women's Health Questionnaire

Duration of the relationship

All the listed studies included only women reporting to be in a stable sexual relationship (of at least 6 months to 1 year).

Frequency of sexual activity

All subjects included in the identified studies were required to have a minimal frequency of sexual activity of at least once a month. Sexual activity prior to the trial was not restricted to a maximum, so women may have been included with a sexual activity of more than once a day during the pre-treatment period.

Concurrent health conditions and disallowed medication

Exclusion criteria in the reviewed trials were comparable and contained the following: sensitivity/contraindications to estrogens and/or androgen therapy, use of androgens in the preceding 3 months, a history of estrogen related cancer, illnesses known to influence sexual function (psychiatric disorders, neurological disease, gynecological cancer), endocrine disorders with systemic disease which would impair overall health and well being (treated hypothyroidism or hyperthyroidism usually allowed), uncontrolled hypertension, sexual or phobic disorders unrelated or related to sexual abuse, medications known to interfere with the trial medication, medications known to impair sexual function (anti hypertensive drugs including β-blockers, anti-depressants), body mass index (BMI) within certain limits, dyspareunia as the primary cause of sexual dysfunction, physical limitations interfering with normal sexual function, angina pectoris and or myocardial infarction in the past (sildenafil trials) and lipid lowering drugs (androgen trials). Some of the trials included women with a BMI above 30 kg/m^2 with a maximum of BMI 35 kg/m^2.[34,36]

Concomitant use of estrogen containing preparations

In the studies of Buster[36] and Simon[38], women were stratified by oral or transdermal estrogen use. The majority of subjects used oral estrogens (75% in the Simon study and 80% in the Buster study). Goldstat[34] included women using oral contraceptives (OAC), but the results were not stratified by OAC use.

Power Calculation

Most but not all of the trials included in this review provided a primary objective and some form of sample size calculation. Only three studies based their sample size calculation on a predefined minimal difference in effect between treatment-groups considered to be clinically relevant.[36-38] These studies included the number of satisfactory sexual events as (co)primary endpoint. The power calculation was based on a difference of 0.34 sexual events per week between the placebo arm and the treatment arm.

Caruso[28] based his sample size calculation on differences found on the erectile dysfunction score in a trial in men.

Other studies included as the primary efficacy parameter the change from baseline on certain scales or subscales (domains) of sexual functioning. In these studies, an adequate power calculation was either not described or was not based on the methods

recommended by Cohen[45]. This is important as most instruments used in these trials were not developed for the measurement of a treatment effect. Scales measuring complex behavior, like sexual functioning, have by definition a low predictive power and briefer questionnaires further compound this problem by their relatively low reliability.[46] Thus only a small to medium effect size for total or composite scores on the sexual function scales can be assumed.

Outcome Measures

Patient reported outcomes

The selection of self-administered sexuality questionnaires included in the reviewed publications is included in Table 1.

Various instruments to assess the level of sexual functioning are currently available and several are considered to be comprehensive and useful and recommended for inclusion in FSD trials.[11,47,48] The following questionnaires have demonstrated acceptable reliability and validity: the Golombok Rust Inventory of Sexual Satisfaction (GRISS; 1987)[49], the Brief Index of Sexual Functioning (BISF; 1994)[41], the Changes in Sexual Functioning Questionnaire (CSFQ; 1997)[42], the Derogatis Interview for Sexual Functioning (DISF-SR;1997)[50], the Index of Female Sexual Function (IFSF; 1999)[51], the Female Sexual Function Index (FSFI; 2000)[52], the Female Intervention Efficacy index (FIEI; 2001)[53], the Sexual Function Questionnaire (SFQ; 2002)[54] and the Female Sexual Distress Scale (FSDS; 2002)[55].

The Profile of Female Sexual Function (PFSF; 2004) which is used in three of the included trials[36-38] was developed very recently and is thus not (yet) included in the recommendations for clinical trials in FSD. However, it shows robust psychometric properties including good inter-item correlations, discriminating ability, test/retest reliability, internal consistency and construct validity.[56,57] The Menopausal Sexual Interest Questionnaire (MSIQ; 2004) was used as one of the primary efficacy outcome measures in the trials of Lobo[33] and Warnock[35] prior to having proven its sensitivity and construct validity. Subsequently, the validity of the MSIQ has been published[57].

Of note: all instruments are still based on the traditional linear model of female sexual function underlying the DSM-IV-R classification which depicts discreet phases and presumes initial or spontaneous desire and ignores subjective arousal. Most questionnaires do not provide clear cut-off scores discriminating women with FSD from women without FSD. Of the available instruments, only the BISF, the SFQ, the FSDS, the FSFI, the FIEI and the PFSF have been developed, or subsequently validated, to be sensitive to a treatment effect.

Of the self-reported questionnaires used in the reviewed studies, only the SFQ was included as a secondary endpoint in phase II studies in order to assess whether a treatment effect could be measured with the scale prior to use it in larger phase III trials as a (co)primary endpoint.[54]

For the other relatively new questionnaires, the intervention study itself was used to investigate whether the scale would respond to change and to further validate the questionnaire (inclusion as secondary endpoint).

Some questionnaires were specifically developed to measure certain aspects of sexual dysfunction like the SFQ (Female Sexual Arousal Disorder) and the PFSF (Hypoactive

Sexual Desire Disorder). These questionnaires are not automatically applicable for trials evaluating a broad spectrum of FSD.
Subject satisfaction with the sexual relationship is only addressed in the BISF and FSFI. The PFSF is the only questionnaire addressing subjective experience of being receptive to sexual cues other than to sexual activity only. None of the questionnaires includes questions pertaining to subject satisfaction with a particular result after treatment.
The frequency of successful satisfactory sexual events, one of the FDA's recommended primary endpoints, was included in 4 of the 11 reviewed trials[31-38] and was measured by a one week recall diary, the Sexual Activity Log (SAL).[59]

Hormone Measurements

As depicted in table 1, all studies of testosterone therapy in this review have included serum hormone measurements to monitor safety. One study used baseline estradiol and androgen measures as inclusion criteria to exclude androgen and/or estrogen insufficiency prior to being randomized to sildenafil.[31] Two studies reported significant positive correlations between changes in serum total, bio-available and free testosterone levels at week 24 and an improvement in measures of sexual function.[36,38] In the testostosterone patch studies total testosterone was measured by radioimmunoassay, bio T by ammonium sulfate precipitation technique, free T by equilibrium dialysis and SHBG by immunoassay.

Study duration and time to treatment effect

For sildenafil, the treatment duration in the studies included varied from 1 hour prior to sexual activity (erotic video) to 12 weeks. For testosterone, the treatment duration varied from 8 weeks to 24 weeks.
If a significant improvement in sexual functioning was identified during the trial period, this was mostly observed after at least 12 weeks of therapy. In the studies of Simon[38] and Buster[36], a statistical significant difference in the frequency of satisfactory sexual events and sexual desire between the two study arms was found after 5 (Buster) to 8 (Simon) weeks and was maintained over the total study period (24 weeks).
Both the study of Shifren[32] as well as the study of Goldstat[34] found a significant improvement at 12 weeks. Mixed results were found in the study of Warnock[35], which can be partially due to the treatment period which was only 8 weeks for the total study period. In the study of the Lobo[33], a statistical significant improvement in sexual desire over placebo was only found after 16 weeks.

Discussion

In the past 6 years, both expert groups and authorities have given guidance to clinicians and researchers how to define FSD (including a new classification system) and how to perform clinical trials in FSD.[6,7,9,11] As the field of FSD is an evolving area of research, continuous adaptations and revisions to definitions and assessment measures have

been made parallel to the conduct of several major trials which in turn have increased our understanding of female sexual function.
This review has identified a number of limitations and issues in drug intervention studies in FSD which should be taken into consideration by anyone doing future research in FSD and which might be addressed in updated guidelines about how to perform intervention trials in FSD.

Defining the population

In spite of a better understanding of female sexual function, the diagnosis of FSD is still very challenging and remains difficult due to its complex nature including several subjective aspects and contextual factors.[60]
There is no internationally accepted screening tool for FSD such that the diagnosis of FSD is based on non-standardized interviews by an expert in the field. In clinical research this can become a problem as due to multiple sites participating, not every center has the same expertise. Recently, cut-off scores to discriminate between normal sexual function and FSD women have been provided for the SFQ[61] and FSFI.[62] In an effort to standardize the diagnosis of FSD and to prevent a wide variability of subjects included in clinical trials, a structured diagnostic method (SDM) has been developed.[63] The SDM can be used by trained interviewers to consistently, and when compared to experts, correctly diagnose FSD status. The SDM consists of four self-reported questionnaires, followed by a structured face-to-face interview. Despite showing high convergent validity and intrarater reliability, this method needs further validation in larger and different patient populations. For sexual functioning, specifically the SFQ and FSDS are included in the SDM. Of note, the SFQ is designed to measure a treatment effect of interventions with a focus on genital arousal disorder.
The FDA draft guidelines require that for inclusion in clinical trials, women must have sexuality related personal distress and can be assessed by the Female Sexual Distress Scale (FSDS) or another validated scale. However, none of the studies in this review used sexuality personal distress as an inclusion criterion. One of the reasons might be that it is difficult to determine what should be the level of distress for an individual woman especially if recruited for a trial, where women are approached via advertisements and not spontaneously seeking medical help for a problem. Not all women who are concerned about their level of sexual desire or arousal have associated feelings of guilt and inferiority (factors in the FSDS) in relation to their sexual concerns. The criterion is somewhat odd as men with erectile dysfunction (ED) are not required to demonstrate distress about their ED to merit therapy.[64,65] In daily practice it should suffice if a woman is sufficiently concerned about her sexual function that she seeks medical advice.
The selection of questionnaires for the SDM is based on the AFUD classification of 2000 which is still based on the traditional linear model of female sexual response.[4] Since then, various papers have been published which have recommended changes[66,67] and recently the AFUD revised her classification system which will influence the design of future questionnaires and diagnostic methods.[7,8,68] To define FSD for inclusion in clinical trials, we recommend reconsidering the selection of (new to be developed) questionnaires included in the SDM based on the current insights about female sexual functioning.

Inclusion and exclusion criteria

Heterogeneity in the study population of FSD trials may influence the outcomes. Allowing broad age limits may complicate the detection of small treatment effects as there is a normative broad range of sexual functioning[1] and a normative lowering with age[2,3,64] which causes large variation in sexual functioning at baseline. In addition, the clinical issues and sexual health needs for young women are likely to be very different from those of older women and this is likely to be further complicated by including young women who have undergone a surgical premature menopause, in whom sexuality might be influenced by other factors such as the premature loss of fertility.

The length of the relationship is predictive for sexual behavior/functioning[70] with recent change of partner being a positively influence[71]. Thus women included in trials with a relationship of more than 10 years in duration are likely to respond differently to intervention for their sexual functioning than women who have had a more short term relationship and report dissatisfaction with their sexlife.

In contrast to men with ED, women will continue to be sexually active even though they lack desire or arousal. Thus a minimal frequency of sexual activity at screening has been required for inclusion in most FSD trials, where as few trials have had an upper limitation. This requirement is based on the assumption that women who have abstained from sexual activity because they have lost interest are unlikely to recommence activity with therapy. There is no data to support this assumption. It is also unclear whether women with a greater baseline frequency of activity are more responsive or refractory to therapy. This needs to be investigated more carefully.

Including women who are obese (BMI greater than 30 kg/m^2) warrants consideration as these women may have the metabolic syndrome and metabolize sex steroids differently when compared to women with a lower BMI. To circumvent this problem a range of SHBG for inclusion should be considered.

Unfortunately, little is known about the influence of many prescribed and non prescribed medications on sexual functioning. Most information is derived from experience from trials of male ED. It is questionable if causalities for ED are applicable for FSD. For instance, the use of thiazide diuretics is highly associated with ED and the use of this drug has not been an exclusion criterion in trials for women. The more selective β1-blockers are not associated with ED [2nd international Consultation on Sexual Dysfunctions-Paris 2003].[48]

From clinical experience, it is assumed that narcotics, including the regular use of codeine (e.g. in flu tablets) influences sexual functioning[72], however, this has not been a standard exclusion criterion in the reviewed trials. From a clinical practical point of view, it is difficult, and may be inappropriate to exclude all women who use medication which is very common in certain age groups (like anti-hypertensive drugs, i.e. β-blockers) as trial outcomes will then never be applicable to the more general population.

The role of the use of hormone therapy (HT) prior to inclusion in the trials has not been clearly defined. Estrogens appear to be important for normal sexual functioning not only for maintaining structural and functional integrity of the vaginal tissues but also for their central brain effects. As a result, there is a prevailing belief that the diagnosis FSD should ideally only be made if a woman is adequately estrogenized. However, this is based on

expert opinion and not on research data. If studies currently underway demonstrate that testosterone therapy in postmenopausal women not on concurrent estrogen is both effective and safe, the issue of requiring a woman to be estrogenized before diagnosing or treating FSD will need to be seriously reviewed.

After menopause, sexual functioning can be negatively influenced by a mixture of climacteric symptoms and it is likely that an improvement in general well-being achieved with symptom amelioration by HT, will positively influence sexual functioning. In clinical trials assessing the efficacy of a certain treatment on sexual function this is important as a real placebo arm will quickly unblind the trial.

On the other hand, oral HT increases SHBG which in turn decreases bio-available testosterone, which might negatively influence sexual functioning. There is also data to suggest that oral conjugated equine estrogen therapy (CEE) interferes with the efficacy of exogenous testosterone.[73] All trials included in this review involved women either with normal estrogen levels or being adequately estrogenized prior to inclusion and many involved women taking oral CEE. It can be discussed whether the oral contraceptives act similar as anti-androgens because they increase SHBG levels resulting in less bio-available testosterone.

Treatment effect

The impetus for treating women who complain of decreased sexual desire or arousal with pharmaceutical interventions like sildenafil or testosterone comes from the assumption that these compounds play a similar role in women' s sexuality as it does in men's. However, female sexual experience is mediated to a certain extent by expectations which are the product of prevailing societal values, familial values and partner expectations. So it can be questioned what exactly is measured in trials attempting to determine the extend to which a single factor, such as drug intervention, modulates sexual function as long as sexual functioning is not placed in an adequate female sexual bio-psycho-social model that includes the role of androgens.

In four trials included in this review for which power was inadequate, (partially) negative results have been found.[29,32,33,35] This does not necessarily exclude an association between the treatment and a parameter of sexual function investigated but may be the result of type 1 error (sample size not large enough to detect a minimal difference).

In a small lab based trial including women diagnosed with genital arousal disorder based on a clinical assessment only, no treatment effect could be found.[30] Also the large trial of Basson et.al., including women with broad spectrum FSD, including FSAD, did not find any treatment effect.[29] Apart from the heterogenous population in the latter trial, which has most likely contributed to the negative results, another explanation might be that the relationship between subjective sexual arousal and genital sexual arousal is poor and that the overlap between desire and arousal may require desire to improve for arousal to improve.[52,75] This might be due to the fact that a woman's subjective experience of sexual arousal is determined less by feedback from her genitals and more by the intensity and appraisal of the sexual stimulus.[76]

The diagnosis genital arousal disorder can only be made if certain conditions, like the presence of adequate sexual stimulation, are met. It is virtually impossible for a clinician

to judge this based on an interview only and the diagnosis genital arousal disorder can possibly only be made under laboratory conditions (erotic video and VPA), where the photoplethysmograph might be useful in further characterization of the genital arousal disorder.[30,77] In clinical practice, the place of vaginal plethysmography is unclear and in most doctor's offices not available.

In seven trials included in this review[28-30,32-35] an improvement in certain aspects of female sexual function was found based on self administered sexuality questionnaires. Whether a statistically significant improvement is clinically meaningful remains a topic of discussion for future trials as currently, a minimal important difference in effect size has not been defined yet for intervention trials in FSD. Another limitation is that the outcomes of most trials in this review are concluded from questionnaires still based on the traditional linear linear sexual response model. For instance, Shifren et.al.[32] measured an "improvement in sexual functioning", Basson et.al.[30] found an "increased subjective sexual arousal and a reduced latency to orgasm" and de Lobo[33] found an increase in sexual desire and interest scores. In spite of the results being interesting and contributing to our understanding of female sexual functioning, it is unclear what these outcomes mean to the individual patient. First of all, a woman's motivation for sexual activity is frequently for reasons other than sexual desire and/or sexual thoughts and fantasies and its absence does not equate to dysfunction.[6,78] Second, emotional well-being and positive emotional responses during sexual activity are reported to contribute more to sexual satisfaction than physical or genital aspects of sexual response.[70,78] So, to maintain a focus on initial or spontaneous sexual desire, fantasies, thoughts when assessing sexual function/satisfaction is not evidence based.
Measuring improvements of sexual functioning in questionnaires showing an increased sexual desire and/or arousal gives no full answer on whether a treatment has been efficacious or not as a higher or lower degree of sexual desire does not form a measure for sexual satisfaction.
The later published studies[36-38] all used a combination of Self Administered Questionnaires (SAQ's) to measure qualitative aspects of sexuality and an event log, like the Sexual Activity Log (SAL), to measure the frequency of successful and satisfactory sexual events. Using the frequency of satisfactory sexual events as an endpoint, the woman herself reports, based on a personal judgment, if she has experienced a certain sexual event (including oral sex, masturbation, intercourse, orgasm) as being satisfactory for her or not.

As this is a subjective assessment, it does not matter what has determined her satisfaction with the event, whether it is due to the improvement in desire or other for instance sexual relationship related or contextual reasons. As in most studies in this review overall sexual satisfaction and satisfaction with the sexual relationship was not evaluated it might be useful, however, to measure patient satisfaction with the sexual relationship and with a particular treatment in future trials.
A limitation of the use of a diary or event log measure is that they are typically completed at home and susceptible to various forms of response bias or error. Other authors

have commented on this and provided suggestions how to improve compliance issues with diaries by using more technically sophisticated methods like electronic diaries or phone call-in methodologies.[11] In addition, diary data are restricted to the scope of measurement and do not provide the broad multidimensional assessment of the response.

A combined approach (using both SAQ's and diaries) seems to be a valid way to assess overall treatment effects of pharmaceutical intervention as both subjective and qualitative aspects of sexuality like desire and arousal are addressed and also the effect of these aspects on sexual function is measured.

For practicing physicians, it would be helpful to understand what a particular significant result (increase in score) means for clinical practice as most trials in this review used different questionnaires which are difficult to compare in the clinical setting.

To inform both women and health care practitioners better what they can expect from a certain treatment, we suggest that a measure like "what percentage of women is satisfied with a specific result or how many of the treated women experienced a 50% or greater improvement in their satisfaction with sexual activity and/or relationship". Goldstat et.al.[34] elegantly described this in her paper by translating the statistical significant improvement of 15.7 units on the Sabbatsberg Sexual Self Rating Scale to terms of meaning for clinical practice which is: 46% of the women experienced a 50% or greater increase in their total sexual self rating score with testosterone treatment.

Another important issue is the cultural acceptance and understanding of questionnaires.

Most questionnaires used in the described trials are validated in women in English speaking countries only (U.S, U.K, and Australia). The PFSF did undergo linguistic validation in several European languages.[56] However in addition to linguistic validation, cultural applicability must also be determined, particularly for application in nonwestern cultures as beliefs with respect to "normalcy" of certain sexual behaviors are highly sensitive to societal beliefs.

For future trials a universally accepted selection of questionnaires and event logs should be used which are based on the current insights and understanding of female sexual functioning.

The patient reported outcome measures (PRO's) should be able to measure a treatment effect, not only in frequency but also in intensity and should be applicable for different cultures. A minimal important difference that should be seen as change over time from baseline between the placebo arm and treatment arm and time to expected treatment effect should be discussed upfront between expert groups and authorities.

Hormone measurements

Although it is widely accepted that sex hormones exert an important influence on sexual functioning, the biomechanism(s) by which hormones operate is poorly understood. There is no evidence that measurement of steroid hormones assist with the diagnosis of FSD.[12,79] Measurement of hormonal levels are primarily indicated to monitor therapeutic safety. One of the difficulties in assessing androgen serum levels is that the range of testosterone to measure in women is very narrow and distinguishing

significant differences is difficult. Free T by equilibrium dialysis is regarded as the gold standard whereas calculation of free T (or calculation of free androgen index) by measuring total T after organic solvent extraction or RIA has been validated in several reports and is recommended as a possible option as well.[80-82]

As intracrinology plays a pivotal role in androgen metabolism, it is likely that behavioral aspects of androgens by tissue metabolism cannot be measured peripherally. It is possible that androgen derivatives measured in serum or urine, are a better reflection of what is happening at a tissue level. This is a subject for future investigation.

Conclusion

In order to be able to measure a treatment effect of the intervention which is clinically meaningful for a woman the following issues need to be resolved prior to initiating new intervention trials in FSD.

A universally accepted method for defining the FSD population is needed and as a result a consensus should be reached for appropriate inclusion and exclusion criteria for FSD trials. Similarly main outcome measures appropriate for the evaluation of drug intervention should be defined. Trial endpoints need to reflect clinically relevant outcomes and should be embedded in a bio-psycho-social sexual response model for women.

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CHAPTER 6

Effects of tibolone and raloxifene on health related quality of life and sexual function

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Abstract

Objectives: Study to compare the effects of tibolone and raloxifene on health related quality of life, sexuality and vaginal atrophy.

Methods: A double-blind, randomized study was conducted in 308 osteopenic, but otherwise healthy, postmenopausal women (mean age 66 years) who received tibolone 1.25 mg/day or raloxifene 60 mg/day for 2 years. Health related quality of life was assessed by the Women's Health Questionnaire (WHQ), sexual function by the McCoy Female Sexuality Questionnaire (MFSQ) and vaginal atrophy by assessing the Karyopycnotic Index (KI) and Vaginal Maturation (VM).

Results: At week 104, the tibolone group showed a trend towards an improved health related quality of life (HRQoL) mean score in eight out of nine WHQ domains. HRQoL scores approximated values for premenopausal women, being pre-defined as "clinically relevant". The raloxifene group showed a trend to a diminished HRQoL mean score from baseline to week 104. No difference could be assessed between the tibolone and raloxifene group in mean total score and separate domains scores of the MFSQ, except for the vaginal lubrication domain ($p= 0.037$). The increase in KI and VM was statistically significantly greater with tibolone than with raloxifene (for both KI and VM $p<0.0001$). Tibolone and raloxifene were equally well tolerated.

Conclusions: In older postmenopausal women, tibolone treatment showed a trend towards an improvement in quality of life and sexuality when compared to raloxifene.

Introduction

The publication of the Women's Health Initiative[1] and Million Women Study[2] studies led to a change in thinking about the use of hormone therapy (HT) for osteoporosis prevention and prompted consideration of other available strategies such as bisphosphonates, parathyroid hormone, selective estrogen receptor modulators (SERMs) and the selective tissue estrogenic activity regulator (STEAR) tibolone.[3,4]

Tibolone regulates estrogenic activity in a tissue selective manner, resulting in estrogenic activity in certain tissues, like bone, vagina and the brain, hereby improving vasomotor symptoms, whilst avoiding it in the endometrium and breast.[5] This tissue selective action of tibolone and its metabolites is a result of a number of mechanisms, depending on the target tissue, and include local metabolism, inactivation or activation of steroid metabolizing enzymes and differential receptor binding.

In contrast, the tissue selective action of the SERMs is solely a consequence of receptor binding which results in estrogenic agonist or antagonist effects, depending on the target tissue. Tibolone therefore differs from the SERMs, not only because it has no antagonistic effect on the estrogen receptor, but also because it acts via a variety of mechanisms.[6]

Efficacy in the prevention and treatment of osteoporosis in postmenopausal women has been confirmed in randomized controlled studies with raloxifene[7-11] and with a standard 2.5 mg/day dose of tibolone.[12-14] A lower dose of 1.25 mg/day tibolone has also proved consistently effective[15-17] and is now considered to be the optimal dose for osteoporosis prevention. Raloxifene has the benefit of reducing the risk of invasive breast cancer, but suggestions that it has beneficial effects on coronary heart disease have not been confirmed.[18]

In common with conventional estrogen and estrogen-progestogen therapy (EPT), tibolone relieves climacteric symptoms and vaginal atrophy[19-22] and there is evidence that is has beneficial effects on sexual function and mood.[23] Unfortunately, SERMs such as raloxifene may cause or exacerbate hot flushes.[8,9,24] This may deter many postmenopausal women, as the most common reason for taking HT is to alleviate climacteric symptoms.

The primary objective of the Study of Tibolone's Effects on osteoPenia (STEP) study was to compare the effects of tibolone 1.25 mg/day and raloxifene 60 mg/day on lumbar vertebrae bone mineral density (BMD) in osteopenic women. These findings have been published elsewhere.[25,26] The secondary objectives include determination of health-related quality of life, sexual function and vaginal atrophy, the results of which are presented here.

Methods

Subjects

Osteopenic, but otherwise healthy, postmenopausal women (aged 60-79 years) were included in this randomized, double-blind, double-dummy, parallel group comparative

study conducted in eight centers in Australia, France, Germany, Italy and the USA. The study was conducted in compliance with the Declaration of Helsinki, International Conference of Harmonisation guidelines and Good Clinical Practice; the protocol was approved by the Independent Ethics Committee or Institutional Review Board of each center. All women provided written informed consent. The women were recruited through investigator's practices, referrals and advertisements in the local press and broadcast media.

Women were included if they had been amenorrheic for at least a year (if the date of last menstruation was unclear because of perimenopausal HT use, HT had to have been used for at least 2 years), were ambulatory, and had a lumbar vertebrae bone mineral density of -2.5 to -1.0 standard deviations of the T-score and a body mass index of >19 to ≤30 kg/m^2. Exclusion criteria included history/presence of malignancy (or current suspicion of malignancy) or thromboembolic disorders, abnormal Pap smear or transvaginal ultrasound (TVUS), undiagnosed abnormal vaginal bleeding in the previous year, uncontrolled hypertension, type I diabetes mellitus, serious decompensated renal or hepatic disease, abnormal laboratory values, X-ray showing symptomatic vertebral fracture, history of bilateral hip replacement, bone disease other than osteoporosis, and use of >20 cigarettes or 4 alcoholic drinks per day. Other reasons for exclusion included current or recent prolonged use of drugs that affect steroid pharmacokinetics, use of anabolic steroids, calcitonin or raloxifene in the last 6 months, use of alendronate or risedronate for >6 months (12 month washout if >6 months), use of etidronate (6 or 12 month washout if used for ≤1 year or >1 year, respectively), use of fluoride for ≥2 weeks, systemic glucocorticoid treatment for >1 month in the past 6 months, a change in thyroid medication in the last 6 weeks, and ever use of estrogen and/or progestin implants. Washout periods were 8 weeks for oral estrogen and/or progestin, 4 weeks for transdermal HT or local estrogen, and 20 weeks for medroxyprogesterone acetate-containing contraceptives.

Treatment

The women were randomized to treatment with oral tibolone 1.25 mg or raloxifene 60 mg once daily for 2 years. Treatment was taken in the evening and a double-dummy technique was used to preserve blinding. Concomitant use of sex hormones or anabolics, hepatic enzyme inducing drugs, cholestyramine, colestipol, coumarin products or medication for osteoporosis (except calcium/vitamin D) was not permitted.

Assessments

Following screening and baseline visits, assessments were performed after 4, 12, 24, 52, 76 and 104 weeks of treatment.

Health related quality of life, assessed by the Women's Health Questionnaire (WHQ) was measured at baseline and each follow up visit. The WHQ is a self-administered questionnaire consisting of 36 items, which are divided into 9 subscales: somatic symptoms, depressed mood, memory/concentration, anxiety/fears, sexual behavior, vasomotor symptoms, sleep problems, menstrual symptoms and attractiveness.[27] Changes from baseline in the various WHQ domains are expressed in terms of clinical relevance when compared to pre-menopausal values, which is the valid standard to analyze the WHQ.

Sexual function was assessed by the McCoy Female Sexuality Questionnaire Short Form (MFSQ) at baseline and at each follow up visit. The MFSQ questionnaire consists out of four domains created from 9 items: sexual interest, vaginal lubrication, orgasm and sexual partner. A global score is based on the sum of all 9 items.[28]
A vaginal smear was obtained at baseline and after 52 and 104 weeks and vaginal atrophy was assessed by the Karyopycnotic Index (KI) and Vaginal Maturation (VM). Vaginal smears were analyzed by a central cytology/pathology laboratory. The percentage of superficial, intermediate and parabasal cells in the smear was determined. The KI was defined as the percentage of superficial cells. VM was calculated by multiplying the percentage of superficial cells by 1, intermediate cells by 0.5 and parabasal cells by 0 and summing the total. VM values ranged from 0, when only parabasal cells were present (atrophic specimen), to 100 when only superficial cells were present (mature specimens). Physical and gynecological examinations, including TVUS and mammography were performed at baseline and after 52 and 104 weeks. Information on possible adverse events was obtained at each visit.

Statistical analyses

Analyses were based on the Intent-to-treat principle (ITT analysis): all subjects treated who had at least one post-baseline assessment were included in the efficacy analysis.
WHQ and MFSQ analyses were performed using the non-parametric Wilcoxon rank test using a complete case analysis (i.e. domain and global scores were only calculated when all the items were available for the subject). Statistical analyses of KI and VM were performed by an Analysis of Variance (ANOVA) model using the last observation carried forward (LOCF) approach. An imputed case analysis was used to account for subjects who did not complete the final visit at week 104. All tests were two sided with statistical significance defined as $P<0.05$. Analyses were performed using SAS 8.2 software.

Results

In total, 310 women with a mean age of 66 years were enrolled and randomized to trial medication of which finally 153 in the tibolone group and 155 in the raloxifene group commenced treatment. The number of subjects at each stage of the study and their baseline demographic characteristics are shown in Figure 1 and in Table 1. There were no relevant differences between the groups. The ITT population consisted of 115 subjects on tibolone and 120 on raloxifene. The study was discontinued prematurely by 52 subjects in the tibolone group and 50 in the raloxifene group, resulting in 101 completers on tibolone and 105 on raloxifene.

Health-related quality of life

Baseline demographic data relating to quality of life, such as marital status, total family income, level of formal education and occupation, were comparable between the two treatment groups. The majority of women were married, retired, had attended primary or secondary high school and rated their health as good.

Tibolone showed statistically significant benefits (lower mean score) over raloxifene on a number of health-related quality of life domains (Table 2): In the raloxifene group, the WHQ vasomotor symptom domain showed consistently higher scores than in the

Figure 1. Subject disposition

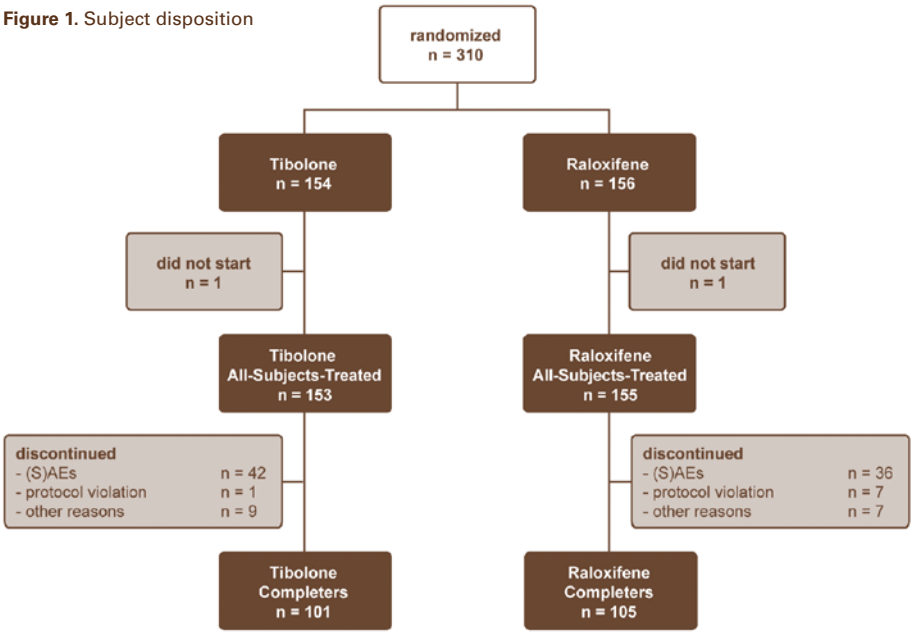


Table 1. Demographic characteristics (AST)

	Tibolone (n=153)	**Raloxifene (n=155)**
Age (years)	66.0 ± 4.6	65.9 ± 4.4
Weight (kg)	66.1 ± 8.7	64.8 ± 8.3
Height (cm)	160.1 ± 6.0	160.7 ± 5.7
Body mass index (kg/m^2)	25.8 ± 2.8	25.1 ± 2.9
Time since menopause (years)	17.4 ± 6.5	17.8 ± 7.0
Number (%) of women who have ever used HT and/or bone agents	65 (42.5%)	63 (40.9%)†
Number (%) of hysterectomized women	40 (26.1%)	41 (26.5%)

†data missing for one women

Values given as mean (±SD) except where stated

tibolone group reflecting a worsening of vasomotor symptoms in the raloxifene group during treatment. The differences were statistically significant at week 12 (p=0.005), week 24 (p=0.001) and week 52 (p=0.002) in favor of the tibolone group. Other domains showing statistically significant differences in favor of the tibolone group included depressed mood at week 24 (p=0.016) and week 104 (p<0.001), sexual behavior at week 52 (p=0.006) and week 104 (p=0.011), somatic symptoms at week 52 (p=0.048) and attractiveness at week 12 (p=0.04). There were no statistically significant advantages for raloxifene on any of the subscales.

No clinical relevant changes based on normative WHQ domain scores for premenopausal women when compared to baseline were found in any of the two groups. However, tibolone treatment resulted in a trend towards an improved quality of life from baseline to week 104 on eight of the nine WHQ subscales: somatic symptoms, depressed mood, memory/concentration, anxiety/fears, sexual behavior, vasomotor symptoms, sleep problems and menstrual symptoms. In contrast, women treated with raloxifene showed a trend towards a poorer health-related quality of life over the same time period on six subscales: somatic symptoms, depressed mood, sexual behavior, vasomotor symptoms, menstrual problems and attractiveness. A clinically relevant "worsening' was found for the attractiveness domain in the raloxifene group from week 52 onwards.

Sexual function

Only 58 (38%)women in the tibolone group and 65 (42%) women in the raloxifene group provided data for the MFSQ. The main reason for not completing this questionnaire was absence of sexual activity. Figure 2 shows the scores in each of the four domains and the total score at baseline and after 52 and 104 weeks of treatment. Generally, there was little to no difference between the tibolone and raloxifene group in mean and median scores for the 4 domains (sexual interest, sex with partner, orgasm and vaginal lubrication) and the global score of the McCoy Female Sexuality Questionnaire, Short Form at any of the post-baseline visits.

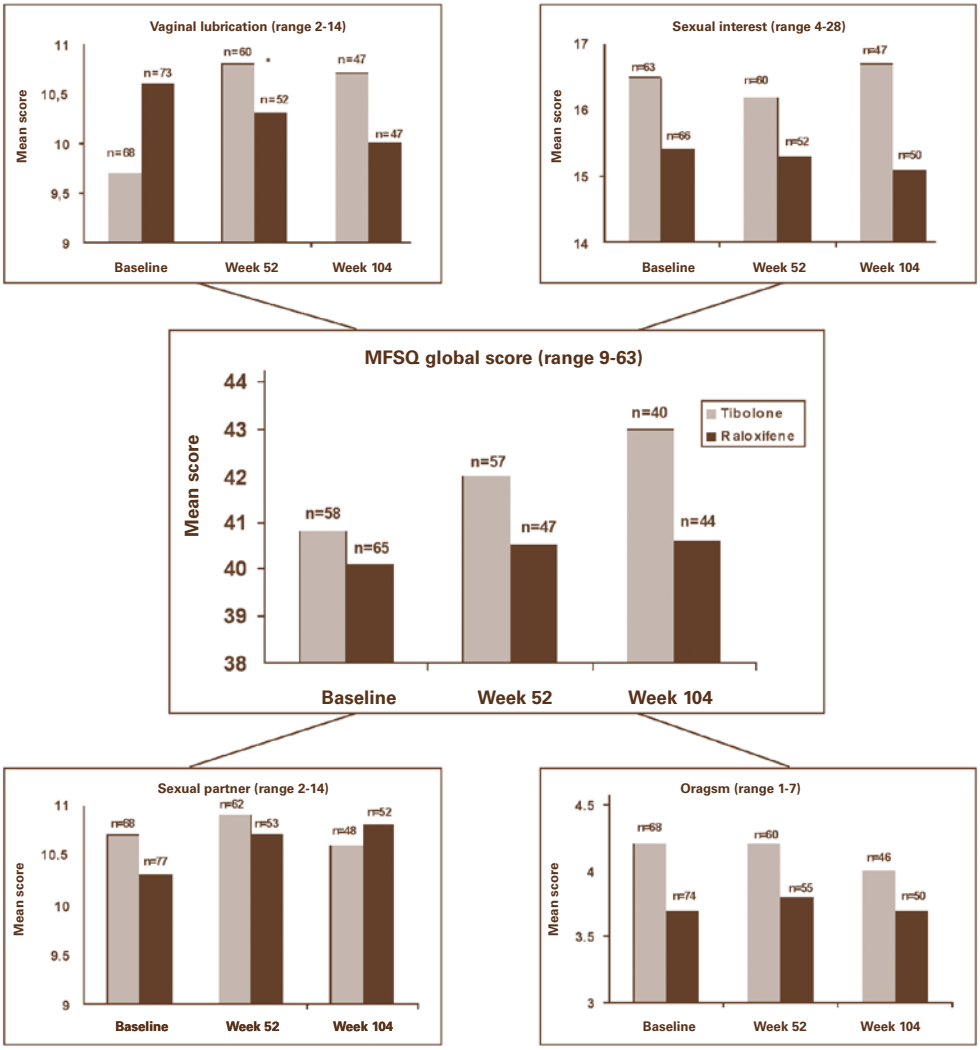
A statistically significant difference in favor of the tibolone group was only found for the vaginal lubrication domain at week 52 where for tibolone a 47% improvement and for raloxifene a 8% improvement from baseline was observed (p=0.037).

A post-hoc separate item analysis showed statistically significant differences in favor of the tibolone treated women on a few questions including the presence of sexual thoughts and fantasies (week 104: p=0.047), feeling aroused/excited (week 24: p=0.038) and a decrease in pain during intercourse (week 52: p=0.02).

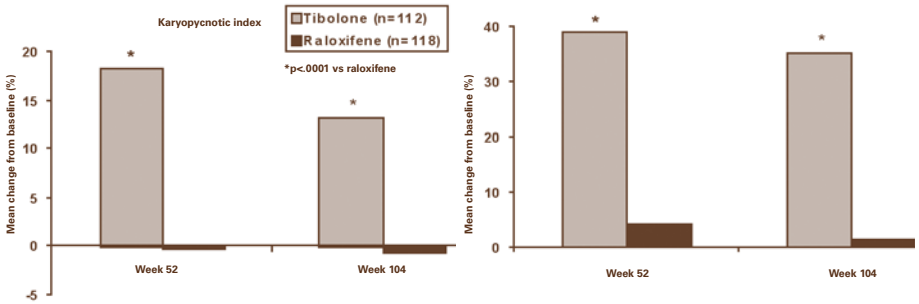
Vaginal atrophy

There were no statistically significant differences between the tibolone and raloxifene groups in baseline KI (4.69% and 4.92%, respectively) or VM (18.06% and 17.74%, respectively). Vaginal atrophy was improved by tibolone, but remained unchanged in the raloxifene group. The increase from baseline in both KI and VM was statistically significantly (p<0.0001) greater with tibolone than with raloxifene after 52 and 104 weeks (Figure 3).

Figure 2. Mean MFSQ actual domain scores and global score (center) at baseline and after 52 and 104 weeks of treatment with tibolone or raloxifene: ITT population (complete case analysis)



Figur 3. Mean change from baseline in Karyopycnotic Index and Vaginal Maturation after 52 and 104 weeks of treatment with tibolone (n=112) or raloxifene (n=118): ITT population (LOCF)



Safety and tolerability

Tibolone and raloxifene were equally well tolerated. The incidence of adverse events (AEs) was similar in both groups. AEs that were reported in >10% of subjects in any or both of the two treatment groups were: muscle spasms (tibolone 25.5%; raloxifene 26.5%), arthralgia (tibolone 16.3%; raloxifene 12.9%), hyperhidrosis (tibolone 13.7%; raloxifene 16.1%), back pain (tibolone 13.1%; raloxifene 11.6%), weight increase (tibolone 12.4%; raloxifene 13.5%), nasopharyngitis (tibolone 11.1%; raloxifene 11.6%), menopausal symptoms (tibolone 10.5%; raloxifene 18.1%), hypertension (tibolone 11.8%; raloxifene <10%), arthralgia (tibolone <10%; raloxifene 12.9%). Adverse events classified as menopausal symptoms (including night sweats and hot flushes) occurred in 23 women (15%) treated with tibolone compared with 37 (24%) treated with raloxifene. AEs accounted for the withdrawal of 27.5% of women in the tibolone group and 23.2% in the raloxifene group; the most common reasons for withdrawal were reproductive system and breast disorders (9.2%), weight increase (3.9%) and gastrointestinal disorders (3.9%) with tibolone and vascular disorders (4.5%) and weight increase (3.2%) with raloxifene. One subject in the raloxifene group died after a fall causing a subarachnoid bleeding. Drug-related (defined as definitely, probably or possibly related to study medication according to the investigators) serious adverse events (each of which occurred in one subject) were postmenopausal bleeding, uterine polyp/vaginal bleeding, endometrial disorder, hydrometra, meningioma, breast cancer and transient ischemic attack in the tibolone group and benign breast neoplasm, dystonia and exanthema/pruritis in the raloxifene group.

There were no clinically relevant differences between the groups with regard to physical and gynecological examinations, cervical Pap smear, TVUS, mammography, vital signs or laboratory parameters. Mean double layer endometrial thickness for tibolone and raloxifene at week 52 were: 1.50 mm and 0.40 mm respectively and at week 104: 1.34 and 0.29 respectively.

Discussion

The recent controversies surrounding conventional HT and the risk of breast cancer and cardiovascular disease have resulted in many women stopping treatment.[29,30] The need remains, however, for effective ways of relieving vasomotor symptoms, improving quality of life and preventing mediate to long term consequences of menopause such as vaginal atrophy and osteoporosis. Amongst the alternative options are the STEAR tibolone and the SERM raloxifene, which have been directly compared in this 2 year study in osteopenic postmenopausal women. Tibolone 1.25 mg/day effectively prevented bone loss and resulted in a larger increase of BMD at the lumbar spine and hip than standard dose raloxifene and less risk of ongoing bone loss from the lumbar spine.[25]

There were a number of other distinctions between the two treatments. Tibolone improved health-related quality of life, with WHQ values approximating those for premenopausal women, whilst women treated with raloxifene showed a trend towards a poorer quality of life.[27] Changes from baseline of a few WHQ domains were statistically significantly larger in favor of the tibolone group when compared to the raloxifene group, particularly the sexual behavior, attractiveness and vasomotor symptoms all showed a statistically significant improvement from baseline. Of note, however, is that results of questionnaires, especially when analyzed at various time points during the study, should be interpreted with caution as a statistically significant difference at only one measured time point without being maintained over the duration of the study and/or without approximating values predefined as being clinically relevant, are likely to be subject to chance. Vasomotor symptoms were consistently worse with raloxifene throughout the study. This was confirmed by the higher incidence of vasomotor symptoms reported as adverse events with raloxifene. Vasomotor effects, which are experienced by more than 80% of untreated postmenopausal women, are often considered the most disturbing symptom of the menopause.[30,31] Although this is the first direct comparison of the efficacy of tibolone and raloxifene in postmenopausal women, studies in estrogen-deficient rats have shown that tibolone, in common with estrogen and clonidine, restored tail temperature to that seen in non-ovariectomized animals, whilst no change occurred with raloxifene.[32] Previous clinical studies have demonstrated that raloxifene causes or worsens vasomotor symptoms, whilst tibolone provides a similar level of relief to that achieved with conventional HT.[19,33,34] The lower 1.25 mg dose of tibolone, as used in the current study, has also been shown to be effective in controlling hot flushes, sweating and other symptoms, resulting in significantly greater relief than that seen with placebo.[21,22]

No statistically significant differences between the two treatment groups regarding changes in sexual function, measured by the MFSQ total score and domain scores, could be observed except for some separate item scores for the tibolone treated women. This is remarkable as it is thought that the reduction in sex hormone binding globulin levels (resulting in increased free testosterone) caused by tibolone, together with the direct androgenic effects of the Δ4 metabolite, contribute to the beneficial effects on sexual well-being reported in previous studies.[23]

In the current study, measures of vaginal atrophy showed improvement with tibolone, whilst there were no meaningful changes in the raloxifene group. Both KI and VM were increased with tibolone, resulting in a significant difference from the raloxifene-treated women. Most likely the improvement in the vaginal lubrication domain of the MFSQ is a result of the improved condition of the vaginal tissue after estrogenic exposure.

Tibolone and raloxifene were equally well tolerated in these elderly postmenopausal women. A number of previous studies have also directly compared various safety and tolerability aspects of tibolone and raloxifene, although all were conducted with the higher 2.5 mg/day dose of tibolone. In this study neither tibolone nor raloxifene were associated with any significant changes in endometrial thickness or unscheduled bleeding/spotting confirming their favorable endometrial profile indicated in previous comparative studies.[35] It must be emphasized that this study was not powered to identify the significance of less common serious AEs, such as VTE and stroke.
A strength of this study is that this is the first randomized controlled study comparing tibolone with raloxifene on various measures of menopausal health in elderly women. In addition we collected sexuality and quality of life data over a longer time period. Limitations of this study are that the actual number of subjects (310) was somewhat lower than the planned number of 325 and that for only one third of the women evaluable MFSQ data were available. For the primary efficacy parameter on bone the difference between groups was large enough to detect a statistical significant difference. However, for the secondary endpoints concerning behavioral science, the study population might not have been large enough to pick up clinically relevant differences especially because quality of life and sexuality are influenced by so many other factors than pharmaceutical treatment only. For the MFSQ analyses the two study groups were not entirely comparable at baseline. As only women who were sexually active completed the questionnaires a selection has taken place which might have prevented to measure more extreme changes in the MFSQ during the trial period. Moreover, the tibolone group had higher baseline scores on the MFSQ. In which way higher or lower scores at baseline influences treatment outcomes is a topic for further investigation.
In conclusion, tibolone showed benefits over raloxifene in certain aspects influencing quality of life which concern: depressed mood, presence of somatic symptoms, improvement of vasomotor symptoms, feelings of attractiveness, improvement of sexual function specifically due to improvement of vaginal lubrication, reduction of painful intercourse, presence of sexual thoughts and improvement of sexual arousal. In addition to the bone preserving effects of both treatments, the above aspects make tibolone an comprehensive treatment for postmenopausal with osteopenia.

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CHAPTER 7

Effects of tibolone versus low dose E_2/NETA on urogenital complaints, sexuality and quality of life in postmenopausul women: results of a randomized controlled clinical trial

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Abstract

Objective: To compare the effects of tibolone 2.5 mg versus E_2 1 mg plus NETA 0.5 mg on sexual function, urogenital complaints and quality of life in postmenopausal women.

Design: a multicenter, randomized, double blind, double dummy group comparative trial. Several questionnaires were used to measure response to therapy: the McCoy sexuality questionnaire for sexual function, the Women's Health Questionnaire (WHQ) for general quality of life and the Urogenital Complaints Scale (LUGCS).

Results: 572 postmenopausal women aged 45-65 years were randomized to the trial. After 48 weeks of treatment, tibolone significantly improved sexual function when compared to E_2/NETA ($p=0.038$). Both treatments resulted in statistically significant improvements from baseline on various urogenital symptoms such as dyspareunia, nocturia, and urgency. A clinically relevant improvement was found for 7 out of 9 WHQ domains in the tibolone treated women and for 5 out of 9 WHQ domains in the E_2/NETA treated women. A statistically significant difference in favor of the E_2/NETA group was found for the vasomotor symptom domain for all visits when compared to tibolone ($p<0.01$).

Conclusions: Tibolone and oral low dose E_2/NETA improve sexual well being by improving various aspects of sexual function and quality of life, the effect being more pronounced with tibolone when compared to low dose E_2/NETA.

Introduction

Tibolone 2.5 mg (Livial®) and low dose continuous combined 1 mg17β-estradiol plus 0.5 mg norethisterone (Activelle®) both registered for the treatment of climacteric symptoms, are currently two of the most prescribed menopausal therapies in Europe. Tibolone is known for its beneficial effects on mood and sexual well-being, vaginal atrophy, urogenital symptoms and bone loss and its endometrial safety and tolerability have been confirmed in large scale randomized controlled trials.[1-5]

A previous study comparing tibolone with continuous combined 2 mg 17β-estradiol (E_2) plus 1 mg norethisterone (NETA) (Kliogest®) indicated that both treatments had a positive effect on sexual well-being.[6] No statistical significant difference between treatment groups could be observed for the change from baseline of the McCoy sexuality questionnaire total score. However, in the same paper a post hoc separate item analysis of the McCoy sexuality questionnaire revealed a statistically significant larger improvement on items such as satisfaction, enjoyment and frequency of sexual activity in favor of the tibolone treated women.

Although tibolone relieves menopausal symptoms and has a favorable tolerability profile, its effects on quality of life (QoI) has not yet been fully established in large randomized controlled trials. In a small placebo controlled study, a trend towards an increased quality of life was found in the group treated with tibolone.[7] Huber et.al., compared tibolone with continuous combined conjugated estrogens combined with medroxyprogesterone acetate (0.625 mg CEE/5 mg MPA), an found an improved QoI for both treatments with no differences between the groups.[8]

Recently the primary efficacy results of the TOTAL trial have been reported including the effects of 2.5 mg tibolone and 1 mg E_2/0.5 mg NETA on vasomotor symptom relief and vaginal bleeding in healthy postmenopausal women.[9] Both treatments significantly reduced vasomotor symptoms and were well tolerated with a comparably low incidence of drug related adverse events. However, treatment with tibolone resulted in a significantly lower vaginal bleeding incidence when compared to E_2/NETA (18.3% versus 33.1% during the first 3 months of treatment $p<0.001$).

The aim of the present study was to assess the effects of tibolone and E_2/NETA in the TOTAL trial on sexual function, urogenital symptoms and quality of life.

Methods

Study participants

Women were eligible to participate if they were aged between 45 and 65 years, had undergone a natural menopause (last menstrual period between 1 and 15 years prior to study entry) and an intact uterus. Women were also required to be in general good health, have a normal mammogram and Papanicoulou smear and a body mass index (BMI) between 18 and 32 kg/m^2. Previous hormone therapy (HT) use was allowed following the applicable wash-out periods specified in the protocol (4 weeks for oral and transdermal HT and tibolone and 6 months for estrogen implants or progestin depot

preparations). Reasons for exclusion were the usual contraindications known for HT and listed in the patient brochure and use of medication expected to affect any of the study outcome parameters or known to interact with steroid metabolism.
The study was conducted in the following countries (number of sites): Norway (11), Sweden (7), Belgium (5), Finland (3), The Netherlands (3), Denmark (2), United Kingdom (1). The study was performed between November 2002 and March 2005.
Each center included between 10 and 25 women. The protocol was approved by the Ethics Committee of each participating study center and written informed consent was obtained from participants before study entry. The study was performed in compliance with the Declaration of Helsinki for Good Clinical Practice.

Study procedures

This double blind, double dummy randomized controlled trial consisted of a 48-week treatment period. After a screening visit at which all subjects underwent a physical examination, a transvaginal ultrasonography (TVUS) and a mammography if a recent (less than 6 months old) mammogram had not been performed, women were randomized in a 1:1 ratio into one of the two study groups via an automatically Interactive Voice Response System (IVRS) using a restricted block-wise randomization. Random permuted blocks were used within each center. The women were treated once daily with either 1 tablet containing 2.5 mg tibolone (Livial®, N.V. Organon, Oss, The Netherlands) or 1 tablet containing 1 mg estradiol plus 0.5 mg norethisterone acetate (Activelle®, Novo Nordisk A/S, Bagsvaerd, Denmark). To enable a double-blind design the double dummy method was applied, with placebo tablets identical in appearance to Livial® or Activelle® to be taken simultaneously with the active treatment. The investigators, study site personnel, and participants remained blinded until after the database was locked.
Study visits were performed at screening and baseline and after 12, 24 and 48 weeks of treatment (Visits 1-3). Non-compliance was defined as missing more than 4 days of medication during a treatment period of 28 days or missing more than 15% of tablets over the entire study period.

Efficacy measures

Sexual function was assessed by the McCoy Female Sexuality Questionnaire Short Form (MFSQ) at baseline and at each follow up visit. The MFSQ questionnaire consists of 9 items grouped into 4 domains: sexual interest, vaginal lubrication, orgasm and sexual partner. A global score is based on the sum of all 9 items and ranges from 9-63 in which a higher score means a better value.[10]
Health related QoL, assessed by the Women's Health Questionnaire (WHQ) was measured at baseline and each follow up visit. The WHQ is a self-administered questionnaire consisting of 36 items, which are divided into 9 subscales: somatic symptoms, depressed mood, memory/concentration, anxiety/fears, sexual behavior, vasomotor symptoms, sleep problems, menstrual symptoms and attractiveness. Changes from baseline in the various WHQ domains are expressed in terms of a clinically relevant change (predefined per separate item) when compared to pre-menopausal values, which is the

valid standard to analyze the WHQ and in which lower values correspond to an improvement of the specific domain.[11,12]

Urogenital complaints were assessed at baseline and each follow up visit with a Local Urogenital Complaints Rating Scale. This scale allows subjects to rate their urogenital discomfort felt in the past month. The vaginal symptoms evaluated by this scale are: pain, dyspareunia, itching, discharge and burning feeling. The urinary symptoms evaluated are: dysuria, frequency, urgency, nocturia, incontinence and urinary tract infection. The possible rating was in five categories: none, mild, moderate, severe and not applicable.

Serum endocrine concentrations of estradiol (E_2), bio-available testosterone (bio-T), total testosterone (total T) and sex-hormone binding globulin (SHBG) were determined for a subset of 200 subjects divided over the centers and the relationship between the total scores and the separate domain scores of the McCoy sexuality questionnaire was assessed as well as the relationship between the serum hormones and the sexual behaviour domain of the WHQ.

Statistical analysis

The analyses were based on the Intent-to-treat principle including all subjects who received at least one dose of study medication and had at least one post baseline assessment of one of the efficacy parameters.

At week 48, questionnaires were evaluated by an Observed Cases endpoint analysis. All statistical tests were performed two-sided and considered statistically significant if $p<0.05$. Post hoc separate item analysis and subgroup analyses were performed to further explore the outcomes of the McCoy sexuality questionnaire.

Sexual dysfunction or sexual problems were no entry criteria in this trial. In order to explore possible differences between women with a self-reported "sub-optimal" sex-life and women who did not report any sexual problem, we divided the data into two subsets. Subset I was the group of women who had reported at baseline a combination of two confirmative answers on the following WHQ items: "I am unsatisfied with my current sexual relationship" and "I have a lost interest in sexual activity" (n=329, for convenience reasons presented in this paper as subset I: women with sexual problems n=329) and women who had not reported a confirmative answer on these WHQ items (n=167, for convenience reasons in this paper presented as subset II: women without sexual problems n=167).

The change from baseline for the nine WHQ domains and the four McCoy domains was compared between the two groups using the Wilcoxon rank sum test.

Analysis of effects on urogenital complaints was done using McNemar's test (to detect changes over time for each treatment group, grouping none/mild and moderate/severe symptoms) and Fisher's exact test (to compare treatment groups).

The correlation between serum hormone levels and outcomes of the sexuality questionnaire were investigated in graphically.

Figure 1. Subject disposition

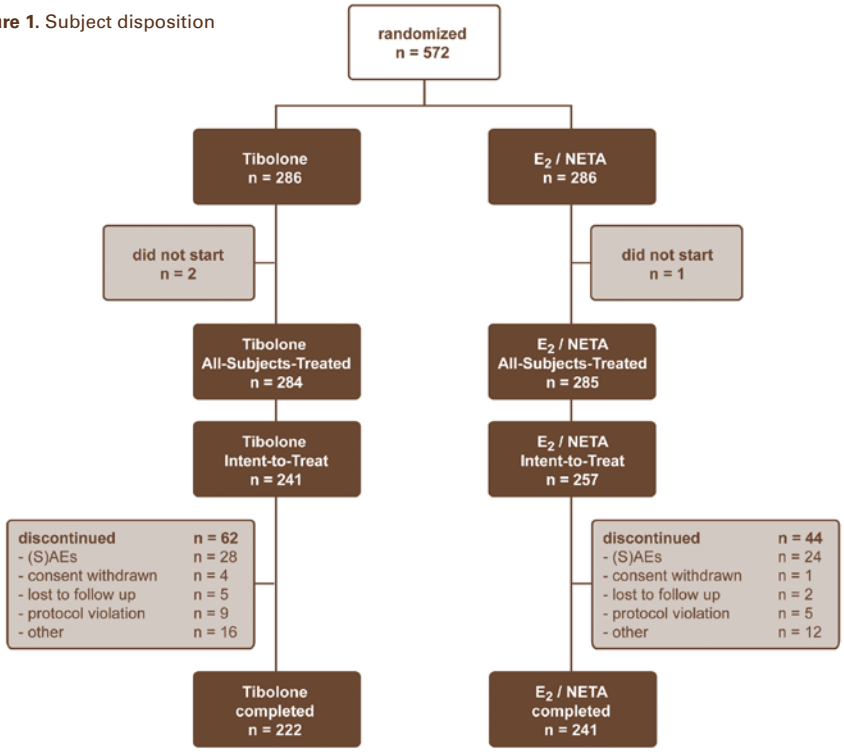
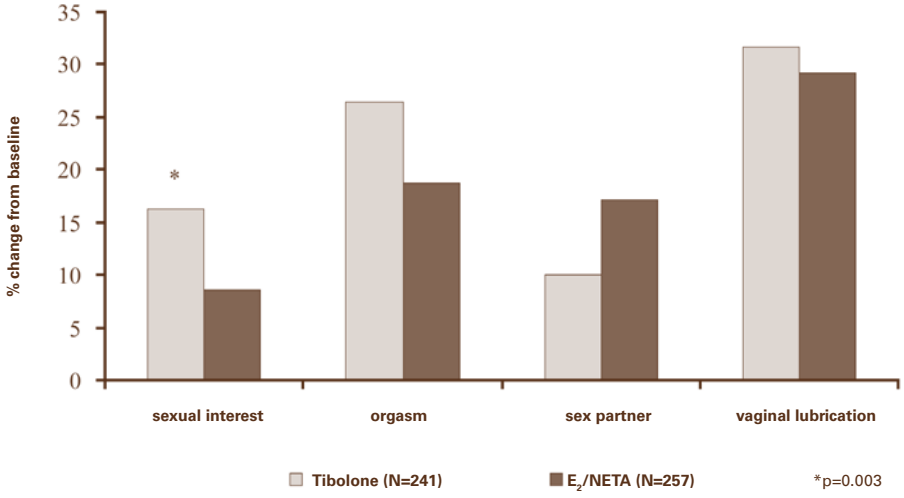


Figure 2. Changes from baseline per treatment group in the 4 domains of the McCoy sexuality questionnaire at week 48 (Intent-to-treat population, endpoint analysis)



Results

A total of 572 women were randomized, of whom 569 actually received treatment (284 in the tibolone group and 285 in the E_2/NETA group). The Intent-to-Treat group consisted of 498 subjects, 241 in the tibolone group and 257 in the E_2/NETA group, respectively. Ultimately, 222 subjects in the tibolone group and 241 in the E_2/NETA group completed the trial (Figure 1). For the baseline demographic data, which were comparable between groups, we refer to the previous report on the same study population.[9]

Sexual function

Both treatment groups showed an improvement from baseline in the separate domain scores as well as the total score of the McCoy sexuality questionnaire. At week 48, a statistically significant difference in favour of tibolone was observed between groups for the McCoy change from baseline total score (p=0.038). This was mainly due to the statistically significant larger increase in sexual interest domain at week 48 was found for the tibolone group when compared to the E_2/NETA group (p=0.003). See Figure 2.

At week 48, improvements from baseline were found for the following separate items (statistical significance marked with an asterix): lubrication (tibolone p<0.001*; E_2/NETA p<0.001*), pain (tibolone p<0.001*; E_2/NETA p<0.001*), frequency of aroused feeling during sex (tibolone p<0.001*; E_2/NETA p=0.165), frequency of orgasm (tibolone p=0.001*; E_2/NETA p=0.038), frequency of sexual thoughts/fantasies during sex (tibolone p=0.011*; E_2/NETA p=0.504), enjoyment of sexual activity (tibolone p<0.001*; E_2/NETA p=0.228), satisfaction with the frequency of sexual activity (tibolone <0.001*; E_2/NETA p=0.062), satisfaction with the partner as a friend (tibolone p=283; E_2/NETA p=0.977), satisfaction with the partner of a lover (tibolone p=0.506 en E_2/NETA 0.377). A significant difference between groups could only be determined for the item "frequency of sexual thoughts and fantasies"(p=0.035) at week 48. Figure 3.

Number of years since menopause significantly correlated with the total scores of the McCoy sexuality questionnaire (i.e. the higher the menopausal age the lower the scores p=0.007).

The change from baseline analyses for women with sexual problems at baseline (subset I) showed significant improvements at week 48 for 3 out of 4 domains (sexual interest, vaginal lubrication and orgasm) and the total McCoy score for both tibolone and E_2/NETA whereas in subset II (women without sexual problems at baseline) a significant improvement from baseline was only found for the vaginal lubrication domain in both treatment groups.

Serum hormone concentrations

The change from baseline in serum hormone concentrations are presented in Figure 4. In the tibolone group there was a decrease from baseline in SHBG and as a consequence an increase in bio-T whereas in the E_2/NETA group there was an increase in SHBG and a decrease in bio T at week 48. Total T decreased in both groups. Serum E_2 significantly increased from baseline in the E_2/NETA group whereas for tibolone no clinically meaningful changes could be observed.

Figure 3. McCoy separate item analysis. Change from baseline per treatment group at week 48 (Intent-to-treat population, endpoint analysis)

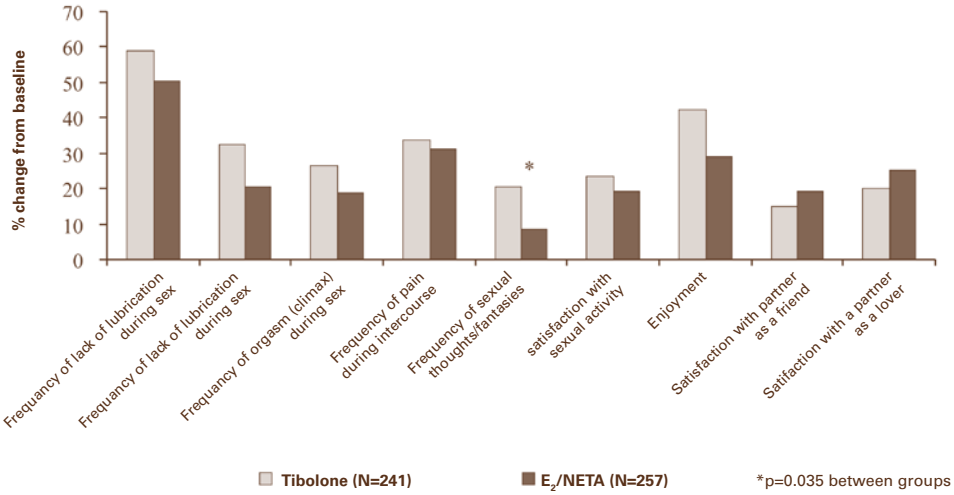
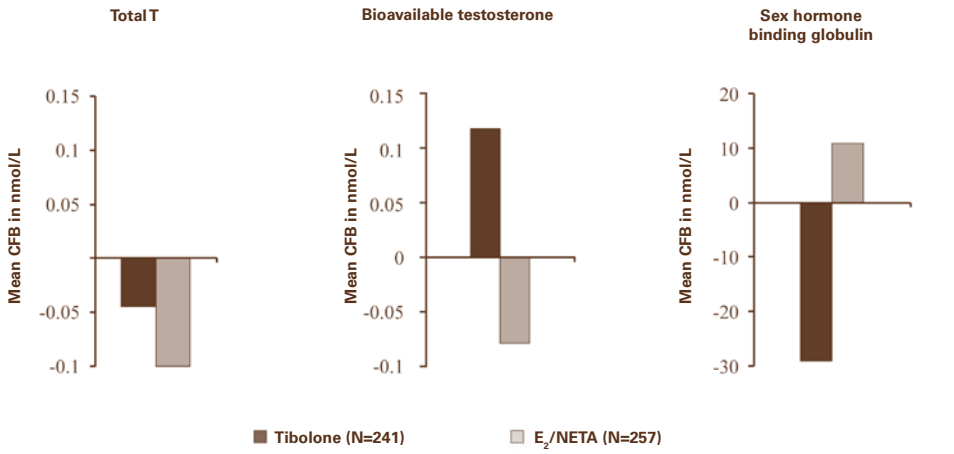


Figure 4. Changes from baseline in serum hormone levels at week 48



None of the individual serum hormone levels at baseline and at week 48 showed any clear correlation with any of the sexual function domains of the McCoy or the sexual behaviour domain of the WHQ.

Health related quality of life

Changes from baseline for each follow up visit in the separate domains of the WHQ are presented in Table 1. At week 48, a clinically relevant improvement was found for 7 out of 9 WHQ domains in the tibolone treated women (somatic symptoms, depressed mood, memory/concentration, anxiety fears, sexual function, vasomotor symptoms and sleep problems). For E_2/NETA a clinically relevant improvement was found for 5 out of 9 domains (somatic symptoms, depressed mood, memory/concentration, vasomotor symptoms and sleep problems) at week 48.

A statistically significant difference in favor of the E_2/NETA group was found for the vasomotor symptom domain for all visits when compared to tibolone ($p<0.01$ for all visits), at week 12 for the dimension "sleep problems" ($p=0.025$) and at week 48 for the dimension "memory/concentration" ($p=0.024$).

The percentage of missing answers on the sexual behavior domain of the WHQ was relatively high (17%). This is explained by the fact that women who were not sexually active did omit the answer on the following question: "As a result of vaginal dryness sexual intercourse has become uncomfortable." At baseline, 50% of the women equally divided over the two treatment groups reported to have lost interest in sexual activity and 25% of the women were not satisfied with their sexual relationship.

Urogenital complaints

The most frequently reported moderate to severe symptoms at baseline were: dyspareunia (10% in the tibolone group and 9% in the E_2/NETA group), frequency (8% in the tibolone group and 13% in the E_2/NETA group), nocturia (9% in the tibolone group and 8% in the E_2/NETA group) and urgency (7% in the tibolone group and 9% in the E_2/NETA group). There were no statistically significant differences between the two treatment groups with respect to efficacy on any of the urogenital complaints. A significant decrease in the number of women experiencing urogenital symptoms when compared to baseline was found for the following items: dyspareunia ($p<0.001$ for both tibolone and E_2/NETA), nocturia (tibolone $p<0.001$ and E_2/NETA $p=0.021$), urgency (tibolone: $p=0.039$ and E_2/NETA: $p=0.002$) and frequency (E_2/NETA: $p<0.001$) at week 48. Table 2.

Table 1. Changes from baseline in actual values of the various domains of the WHQ per treatment group (Intent-to-Treat population)

		Tibolone 2.5 mg (N = 241)	1 mg E_2/ 0.5 mg NETA (N=257)
Domain	**Actual visit**	**Mean (SD)**	**Mean (SD)**
Somatic symptoms (Norm value: 0.38) (Relevant change: 0.06)			
Baseline		0.373 (0.23)	0.385 (0.25)
Change from baseline	Week 12	-0.088 (0.219) #	-0.096 (0.192) #
	Week 24	-0.084 (0.225) #	-0.090 (0.208) #
	Week 48	-0.110 (0.221) #	-0.102 (0.219) #
Depressed mood (Norm value: 0.30) (Relevant change: 0.05)			
Baseline		0.222 (0.227)	0.225 (0.239)
Change from baseline	Week 12	-0.068 (0.212) #	-0.083 (0.212) #
	Week 24	-0.092 (0.207) #	-0.082 (0.213) #
	Week 48	-0.078 (0.201) #	-0.087 (0.233) #
Memory/concentration (Norm value: 0.37) (Relevant change: 0.10)			
Baseline		0.459 (0.381)	0.436 (0.391)
Change from baseline	Week 12	-0.140 (0.334) #	-0.136 (0.316) #
	Week 24	-0.132 (0.341) #	-0.140 (0.317) #
	Week 48	-0.110 (0.346) #	-0.170 (0.348) # *
Anxiety/fears (Norm value: 0.30) (Relevant change: 0.06)			
Baseline		0.234 (0.264)	0.214 (0.271)
Change from baseline	Week 12	-0.087 (0.240)#	-0.056 (0.228)
	Week 24	-0.088 (0.211)#	-0.055 (0.205)
	Week 48	-0.079 (0.243)#	-0.053 (0.226)
Sexual function (Norm value: 0.44) (Relevant change: 0.18)			
Baseline		0.405 (0.382)	0.416 (0.365)
Change from baseline	Week 12	-0.145 (0.361)	-0.138 (0.312)
	Week 24	-0.176 (0.340)	-0.156 (0.312)
	Week 48	-0.199 (0.343) #	-0.153 (0.316)
Vasomotor symptoms (Norm value: 0.47) (Relevant change: 0.20)			
Baseline		0.857 (0.305)	0.835 (0.330)
Change from baseline	Week 12	-0.515 (0.453) #	-0.693 (0.407) # *
	Week 24	-0.575 (0.459) #	-0.697 (0.421) # *
	Week 48	-0.589 (0.443) #	-0.697 (0.412) # *
Sleep problems (Norm value: 0.46) (Relevant change: 0.12)			
Baseline		0.562 (0.346)	0.535 (0.327)
Change from baseline	Week 12	-0.137 (0.316) #	-0.219 (0.333) #
	Week 24	-0.186 (0.356) #	-0.212 (0.351) #
	Week 48	-0.589 (0.443) #	-0.697 (0.412) #
Menstrual symptoms (Norm value: 0.25) (Relevant change: 0.08)			
Baseline		0.195 (0.230)	0.211 (0.261)
Change from baseline	Week 12	-0.005 (0.232)	-0.006 (0.272)
	Week 24	-0.050 (0.232)	-0.046 (0.268)
	Week 48	-0.062 (0.223)	-0.057 (0.263)
Attractiveness (Norm value: 0.58) (Relevant change: 0.07)			
Baseline		0.382 (0.378)	0.389 (0.359)
Change from baseline	Week 12	-0.011 (0.343)	0.034 (0.361)
	Week 24	-0.043 (0.293)	0.039 (0.350)
	Week 48	-0.051 (0.336)	0.023 (0.358)

Norm. value = Normative value of post-menopausal women
Relevant change = Difference in normative value between post- and pre-menopausal women
Clinically relevant change from baseline
* p-value < 0.05 between treatment groups in favour of E_2/NETA assessed by two-sided Wilcoxon rank sum test stratified by center for treatment differences on change from baseline.

Table 2. Results of the McNemar test on local urogenital complaints (symptoms versus no symptoms) for changes from baseline within groups at week 48

	Baseline				Week 48					
	Tibolone (N=237)		E_2/NETA (N=253)		Tibolone (N=229)			E_2/NETA (N=210)		
	n	%	n	%	n	%		n	%	
dyspareunia	24	10.1	23	9.1	1	0.5	p<0.001	4	1.7	p<0.001
nocturia	22	9.3	21	8.3	5	2.4	p<0.001	7	3.0	p=0.021
frequency	19	8.0	33	13.0	8	3.8	p=0.057	10	4.3	p<0.001
urgency	16	6.8	22	8.7	7	3.3	p=0.039	6	2.6	p=0.002

Discussion

The TOTAL study is the first randomized controlled comparative study between tibolone and low dose continuous combined 17β-estradiol plus norethisterone acetate investigating the effects on sexual function, health related quality of life and urogenital complaints in healthy postmenopausal women. Both treatments had an added benefit to healthy postmenopausal women treated for climacteric (mainly vasomotor) symptoms as both tibolone and E_2/NETA showed improvements in sexual function and urogenital complaints and a clinically relevant improvement in health related quality of life when compared to baseline.

Although women in our trial were not identified with sexual dysfunction per se, it seems reasonable, in view of the baseline answers reported at the WHQ and McCoy questionnaire, to assume that approximately half of them experienced mild to moderate sexual problems. Treatment with tibolone or E_2/NETA does not only improve sexual function, including sexual interest, an improved vaginal lubrication and a decrease in dyspareunia, but also several quality of life aspects which might indirectly influence sexuality such as improved sleep and mood as assessed by the WHQ. The total effect of treatment could thus be classified as an improvement in "sexual well-being".

Overall, tibolone had a more pronounced effect on sexuality than E_2/NETA and caused a statistically significant larger increase on the total score of the McCoy sexuality questionnaire and specifically on the sexual interest domain, when compared to low dose E_2/NETA. In addition, a clinically relevant improvement of the sexual behaviour domain of the WHQ (satisfaction with the sexual relationship) was seen in the tibolone treated women but not in the E_2/NETA group.

These findings are clinically relevant as a lack of sexual interest and a decreased satisfaction with the sexual relationship is a complaint, which is commonly reported by

postmenopausal women.[13] Moreover, the finding corresponds to findings from previous studies and might be contributed to the indirect effect of tibolone on androgen levels since these are reported to play a role in motivational aspects of sexuality.[1,6,14,15]

The effects of tibolone on sexual function have also been explored in two different subgroups: women with and without sexual problems at baseline as assessed by the WHQ sexual behaviour domain. It appears that the positive effect of tibolone on sexual function is more notable in the subgroup with sexual problems at baseline. Not sur-prisingly these subjects have lower McCoy total scores at baseline which also opens the possibly for more improvement and thus a larger treatment effect.

It is meanwhile known that no single endogenous hormone level corresponds to female sexual function.[16] We were unable to detect a relation between the improvement in sexual function assessed by the McCoy questionnaire and the circulating exogenous serum hormones as a result of treatment. As we used a valid approach to measure bio-T, employing sensitive non-commercial assays,[17] this negative finding confirms the current understanding that clinical outcome is difficult to predict from androgen blood levels, which probably do not reflect androgen action at the individual's tissue level. However, some of the recently published testosterone patch studies showed a relation between clinical outcome concerning sexual function and circulating testosterone.[18,19] So another reason for not being able to find a correlation might be that the measure of sexual function (McCoy questionnaire) is not sensitive enough to detect changes in sexual function which could be a result of hormonal fluctuations.

Various outcomes relating to health related quality of life (WHQ) showed a clinically relevant improvement in each of two treatment groups. For the domains such as "menstrual symptom" and "attractiveness" no clinically relevant improvement could be observed. This is probably due to the better (lower) baseline scores in these domains when compared to the norm values for postmenopausal women making it very hard if not impossible to find any improvement.

For similar reasons, it is likely that we did not find statistical improvements on some of the items of the urogenital complaint scale. Additional factors that might play a role are the small numbers of the women with symptoms and the skewness of the data.

A strength of this study is the relatively long follow up time as most HT comparative trials on efficacy and/or bleeding have a duration of 12 weeks.

A weakness of the trial is the lack of a placebo arm which ideally should have been included to measure the effect of HT and tibolone on quality of life and sexual function. However, for trial integrity reasons this was not possible as the trial would have been un-blinded by irregular vaginal bleeding in the active treatment arms. Another weakness is that the McCoy sexuality questionnaire may not be the most appropriate tool anymore to assess the treatment effect of HT on sexual function as the questionnaire does not cover the current definition and insights of female sexual dysfunction (FSD)[20] and addresses items which are not likely hormonal dependent such as sex with a partner and orgasm. Recently, Nappi et.al. published the first study in which women identified with FSD were treated with tibolone versus oral cc E_2/NETA.[21] In that trial both treatments increased clitoral circulation measured by Doppler ultrasonography and sexual function measured by the McCoy sexuality questionnaire the effect being significantly larger for

tibolone than for cc E_2/NETA. Interestingly, the mean baseline McCoy score in that trial were similar to those reported in our trial in spite that trial having included women with FSD, a population of which one would expect to correspond with lower baseline values at the McCoy sexuality questionnaire. Another weakness is that a partial placebo effect of both treatments on sexual function cannot be ruled out. However, at all follow up visits an increase from baseline of the McCoy questionnaire was seen which cannot be explained by a placebo effect only, as the trial duration was long enough to see a regression to the mean in case of a substantial placebo effect.

Conclusion: Tibolone and oral low dose E_2/NETA improve sexual well being by improving various aspects of sexual function and quality of life, the effect being more pronounced with tibolone when compared to low dose E_2/NETA.

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CHAPTER 8

Tibolone and transdermal E_2/NETA for the treatment of Female Sexual Dysfunction in naturally menopausal women: results of a randomized active-controlled trial

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Abstract

Introduction: There are some data to suggest that tibolone improves sexual function in postmenopausal women. However, evidence about the effects of tibolone on female sexual dysfunction (FSD) is lacking.

Aim: To compare the efficacy on sexual function of tibolone 2.5 mg to continuous combined transdermal E_2/NETA (50 µg/140µg) in naturally postmenopausal women with sexual dysfunction.

Main outcome measure: Differences between treatment groups in the change from baseline for the composite sub-score of the arousal, desire and satisfaction domains of the self-reported FSFI (Female Sexual Function Index).

Method: The LISA study was a multicenter, randomized, double-blind, double-dummy, controlled trial. Sexual function was assessed with the FSFI at baseline, week 12 and week 24. Outcomes of the Female Sexual Distress Scale (FSDS) and the frequency of satisfying sexual events (daily diaries) were secondary endpoints.

Results: 403 women, mean age 56 were included. Both therapies improved sexual function assessed by the FSFI. In the per-protocol analysis, but not in the Intent-To-Treat analysis, the increase in FSFI scores was significantly larger in the tibolone group when compared with the E_2/NETA patch group at week 24 ($p=0.036$ and $p=0.025$ for the composite sub-score and total FSFI score respectively). The satisfying sexual event rate increased from 3 to 4 times per 28 days at week 24 ($p<0.001$ from baseline for both groups), with no difference between groups. The FSDS showed a significant decrease from baseline ($p<0.001$) which was comparable for both treatment groups.

Conclusion: Both treatments improved overall sexual function as determined by scores on the FSFI, an increase in the frequency of sexual events and a reduction in sexuality related personal distress. The statistically significant higher FSFI scores in the tibolone group when compared to the E_2/NETA group may be due to tibolone's combined oestrogenic and androgenic properties.

Introduction

Since its first introduction to the market in 1988, more than 400 clinical studies on tibolone have been published (source: Medline 1980-2006) and tibolone remains currently one of the most commonly prescribed menopausal therapies in Europe.[1,2]

Tibolone, a selective tissue oestrogenic activity regulator, is metabolised in the gastrointestinal tract to the 3α and 3β metabolites which then circulate predominantly in their sulphated inactive forms.[3] These metabolites become oestrogenically active when desulphated in target tissues. The global effect of tibolone would thus be expected to be oestrogenic. However tibolone itself and its 3β metabolite can be converted to a Δ4-isomer which is able to bind and transactivate the progesterone receptor (PR).[4] In this way tibolone alleviates climacteric symptoms without stimulating the endometrium.[3,5]

There are some data to suggest that tibolone may improve sexual function, particularly sexual desire and arousal, to a greater extent than traditional oestrogen-progestin (E+P) therapy in healthy postmenopausal women.[6,7] These effects have been attributed to the intrinsic capacity of the Δ4-isomer to activate the androgen receptor[8] and to the reduction in sex hormone binding globulin (SHBG) and hence the increase bio available testosterone seen with tibolone therapy.[9]

However, evidence that tibolone is more likely to restore sexual wellbeing than conventional E+P therapy in postmenopausal women presenting with female sexual dys-function (FSD) is lacking.

As sexual dysfunction is common amongst postmenopausal women[10-12] and preferential prescribing of tibolone to such women is widespread, the present study was designed to investigate the effects of tibolone versus a transdermal oestradiol (E_2)/norethisterone acetate (NETA) formulation in naturally postmenopausal women identified as having FSD.

Methods

Subjects

Women were eligible to participate if they were aged between 48 and 68 years, had undergone a natural menopause, had an intact uterus and reported that, prior to the menopause their sex life was satisfying, but that since the menopause they had experienced a decline in satisfaction with sexual activity that was associated with personal distress as measured by the Female Sexual Distress Scale (FSDS score ≥ 15).[13] FSD was defined according to the DSM IV-R classification as persistent or recurring reduction of sex drive or aversion to sexual activity, difficulty becoming aroused, inability to reach orgasm and pain during sexual intercourse in the presence of adequate stimulation. Women were also required to be in general good health, have a normal mammogram and Papanicoulou smear within 6 months prior to enrollment, have no physical impediment to sexual function and to be in an established sexual relationship of at least 6 months in duration with a partner who was sexually functional. Women were excluded if they had other conditions that could have an impact on sexual function, including dyspareunia, any serious disease or disorder or any endocrine disorder with systemic

disease which would have impaired overall health and well being and psychiatric disorders (including depression defined as a Centre for Epidemiologic Studies Depression-scale score of >16)[14], or were taking medications known to affect sexual function such as anti-depressants, narcotics (including regular use of codeine), anti-psychotics. Women were also excluded if they had a history or presence of liver or renal disease, breast cancer or oestrogen- dependent tumours, cardiovascular disease, cerebrovascular disease or thromboembolic events or major gynaecological surgery in the preceding 3 months. Previous unsuccessful use of testosterone or testosterone combinations or compounds known to enhance androgenic activity such as tibolone, dehydroepiandrosterone (DHEA) or transdermal oestrogen–norethisterone therapy, also resulted in exclusion. Previous successful use of the above androgenic treatments or depot oestrogen plus progestin preparations were allowed following the applicable wash-out periods specified in the protocol. Oral oestrogen plus progestin therapy was allowed prior to randomisation. The study protocol was approved by the Independent Ethics Committee of each study centre and the study was performed in compliance with the Declaration of Helsinki (2000 edition).[15] All women gave written informed consent to participate. The trial was registered at www.clinicaltrials.gov

Procedures

Women were recruited via hospital advertisement and local newspaper advertisements to this 24-week double-blind, double-dummy, randomised group comparative study between June 2004 and November 2005 at 29 study centres in 6 European countries, the United States and Australia.

Eligible women were allocated in a 1:1 ratio using a computerized automatic Interactive Voice Response System to treatment with either E_2(50µg)/NETA(140µg) in the form of a twice weekly patch plus a daily placebo tablet or tibolone 2.5 mg as a daily tablet with a twice weekly placebo patch. Placebo patches and tablets were identical in appearance to the active trial medication. The investigators, study site personnel, and participants remained blinded until after the database was locked.

After a screening visit and a 4-week pre-treatment period, assessments were performed at baseline, week 12 and week 24.

Outcome measures

The Female Sexual Function Index (FSFI) is a 19-item self-administered questionnaire that assesses sexual functioning in women using six separate dimensions (desire, arousal, lubrication, orgasm, satisfaction and pain), as well as providing a total score.[16]

The primary efficacy endpoint was defined in the protocol as the change from baseline in the composite score for the domains of desire, arousal and satisfaction of the FSFI in women treated with tibolone versus those given transdermal E_2/NETA.

Secondary efficacy endpoints included comparisons between the treatment groups of changes in the total and the individual domain scores of the FSFI, the level of distress associated with sexual function (measured by the FSDS) and the 4-week sexual activity assessed by a daily diary completed in the 4 weeks prior to randomization and daily during the 24 week study period. Women used the diary to record the frequency of all

sexual activity, whether the activity was satisfying to her (yes or no), the frequency of sexual thoughts and/or fantasies, the frequency of experiencing sexual arousal, the frequency of initiating sexual activity and the frequency of a woman refusing the initiative of her partner for sexual activity. The Women's Health Questionnaire (WHQ) was used to measure general and health related well-being.[17,18]
All questions were presented in the subjects own language. The questionnaires were translated and linguistically validated by an internationally accepted translation methodology performed by the MAPI Research Institute (Lyon, France).[19]

Hormone measures

Morning serum samples were collected between 8.00 and 12.00 a.m at baseline and after 24 weeks of treatment to measure follicle stimulating hormone (FSH), 17β oestradiol (E_2), total testosterone (total T), free T (free T), DHEA sulphate (DHEAS) and sex hormone binding globulin (SHBG) using validated immunoassay methods (BARC, Belgium). Serum concentrations of FSH, E_2, SHBG and total T were determined by ElectroChemiLuminescent ImmunoAssay (ECLIA, Roche Diagnostics) and DHEAS was measured by radioimmunoassay (RIA, Immunotech).
Free testosterone was calculated using values for total T, SHBG and a fixed albumin concentration of 40 g/l, by the Södergard equation.[20,21]
The detection limits and coefficients of variation (CV) were for FSH: 0,1 mIU/mL, CV=2,5% at 55 mIU/mL; E_2 5,0 pg/mL, CV= 4.6% at< 100 pg/mL and 2.9% at >100 pg/mL; testosterone:2 ng/dL, CV=6,5% at < 100 ng/dL and 2.8% at > 100 ng/dL; DHEAS 10 µg/dL, CV=8.7% at 66.1 µg/dL; SHBG 1 nmol/L, CV=2.9 % at 40 nmol/L.

Adverse events

Adverse events were documented from the time of first medication use until subjects exited the trial. All adverse events were categorised using the Medical Dictionary for Regulatory Activities coding dictionary (MEDRA).

Statistical Analysis

Assuming a two-sided test, at the 0.05 α level, it was estimated that a minimum of 286 subjects (143 per group) would be required to provide approximately 80% power to detect a standardized difference in treatment effect of 20% on the composite score (CS) of the FSFI between the two treatment groups. It was therefore aimed to recruit 358 subjects allowing for a 20% discontinuation rate during the 24 week treatment period.
All analyses were performed using the intent-to-treat (ITT) approach, i.e all subjects who had at least one post-baseline assessment. An additional per-protocol (PP) analysis was undertaken for the primary efficacy parameter after exclusion of women with major protocol violations who had continued the trial erroneously. Major predefined protocol violations included: non-compliance with the study medication which would have been a reason for study discontinuation (defined as 6 or more tables missing and/or omission to administer or change the patch twice or more within a period of 4 weeks prior to the study visit), violations of the inclusion and/or exclusion criteria that may have influenced the primary efficacy parameter and partners who did not stay sexually functional during

the trial period. The PP group was defined before un-blinding. Analyses were performed using SAS 8.2 software.

The primary efficacy endpoint was assessed by an analysis of covariance with correcting factors for baseline and center. A last value under treatment (LVUT analysis) was used to account for subjects who did not complete the final visit at week 24 and the Wilcoxon rank sum test was used if the assumptions for normality were violated.

Diary data, including the frequency of satisfying sexual events, were evaluated by Poisson regression analysis.

For the nine subscales of the WHQ, the change from baseline within the treatment groups was analysed by means of the t-test or, if the assumptions for normality were violated, the Wilcoxon rank sum test. The number of adverse events and the percentage of women discontinuing the trial due to adverse events were summarised per treatment group.

Table 1. Baseline characteristics of the treatment groups

Parameter	transdermal E_2/NETA 50 µg/140 µg (n=201)	tibolone 2.5 mg (n=199)
Age (y)	55.8 (4.3)	55.8 (4.4)
Body mass index (kg/m^2)	24.7 (3.3)	25.0 (3.3)
Previous E+P use	45%	52%
Gynaecological surgery	19%	18%
CES-D score[a]	7.7 (6.9)	6.7 (5.3)
Baseline score FSDS[b]	23.9 (9.0)	23.7 (9.3)
Baseline scores FSFI[c] domains		
Desire	2.10 (0.80)	2.07 (0.80)
Arousal	2.67 (1.20)	2.72 (1.19)
Lubrication	2.96 (1.58)	3.15 (1.56)
Orgasm	3.03 (1.60)	3.05 (1.55)
Satisfaction	3.38 (1.18)	3.37 (1.15)
Pain	4.24 (1.88)	4.34 (1.89)
Total	18.4 (6.1)	18.6 (5.8)
Baseline total sexual activity (events/28 days)	5.6 (4.42)	5.7 (4.23)
Baseline frequency of total satisfactory sexual activity (events/28 days)	3.1 (2.72)	3.3 (3.22)

Data shown are mean (SD), unless otherwise noted.

a: The total score range for this test is 0-60, with a score >16 indicative for depressive disorder.

b: The total score range for this test is 0-48, with a cut-off score ≥ 15 being indicative for sexuality related personal distress.

c: The total score range for this test is 2-36, with a cut-off score <26 being indicative for FSD

Results

The baseline characteristics of the study participants, which were comparable in both groups, are shown in Table 1.

Figure 1 summarizes the flow of the study participants. Of the 403 women randomised, 293 (73%) completed the 24-week treatment period. 18 women in the E_2/NETA group and 17 in the tibolone group were not included in the PP analysis due to major protocol violations being: a partner being not sexually functional and/or severe non-compliance with the study medication. 57 women in the E_2/NETA group and 43 women in the tibolone group discontinued the trial prematurely, un-acceptable vaginal bleeding in the E_2/NETA group being the main factor for early discontinuations.

Effects on sexual dysfunction

Female Sexual Function Index

Both therapies resulted in a significant improvement in the composite sub-score of the FSFI at 24 weeks, the primary study outcome. The greater increase in this score with tibolone compared with E_2/NETA approached statistical significance in the ITT analysis (p=0.065) and was significant in the PP analysis (p=0.036). The total FSFI score also increased significantly more with tibolone treatment than with the E_2/NETA patch in the PP analysis (p=0.025), although no significant difference was apparent in the ITT analysis (p=0.092, Table 2a). All of the individual domain scores of the FSFI were statistically significant improved from baseline in both treatment groups, with no differences between the groups. Figure 2 shows the changes from baseline in percentages for each of the separate domains of the FSFI.

Female Sexual Distress Scale

There was a statistically significant reduction in sexuality-related personal distress in both treatment groups when compared to baseline (p<0.001 for both groups). No differences were observed between the groups.

Daily diary

Both treatments also resulted in a statistically significant increase from baseline in the 4-week-frequency of total satisfying sexual activity, with no statistical significant difference between the groups. The mean change from baseline was +1.44 in the tibolone group (+44%; p<0.001) vs. +1.48 in the E_2/NETA group (+45%;p<0.001). (Table 2b)

A statistically significant increase in the frequency of taking the initiative for sexual activity and a significant reduction in refusal of the initiative of the partner was seen, compared with baseline, in both groups. However, there was a greater reduction in refusal of the initiative of the partner in favour of tibolone-treated women compared with E_2/NETA-treated women (-45% vs. -28%; p<0.001). A significant increase in sexual arousal compared with baseline was seen in the tibolone group (+ 23%; p<0.01).

Figure 1. Patient disposition

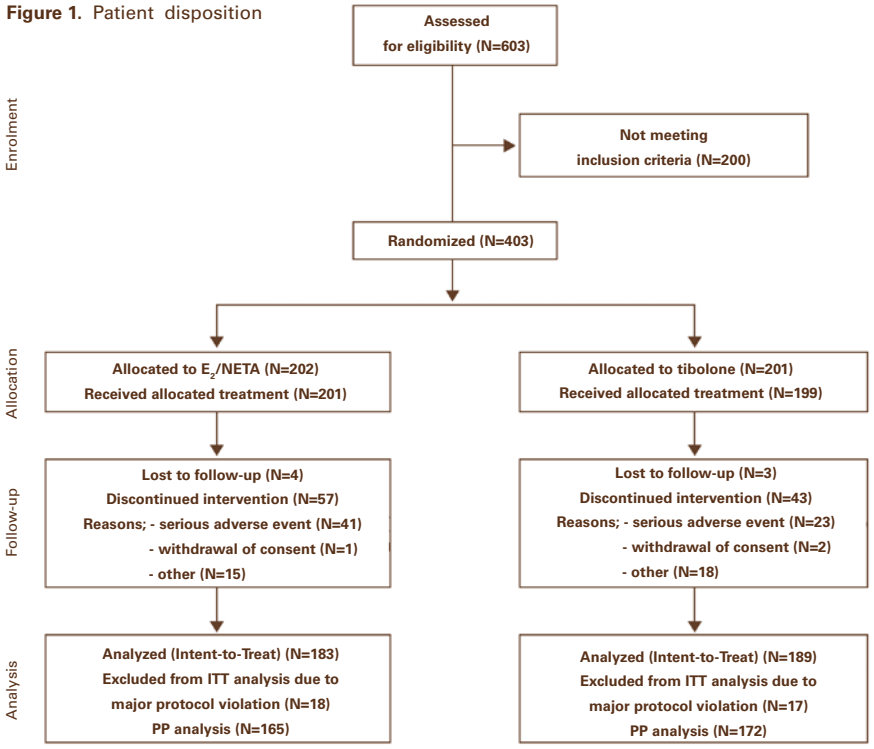
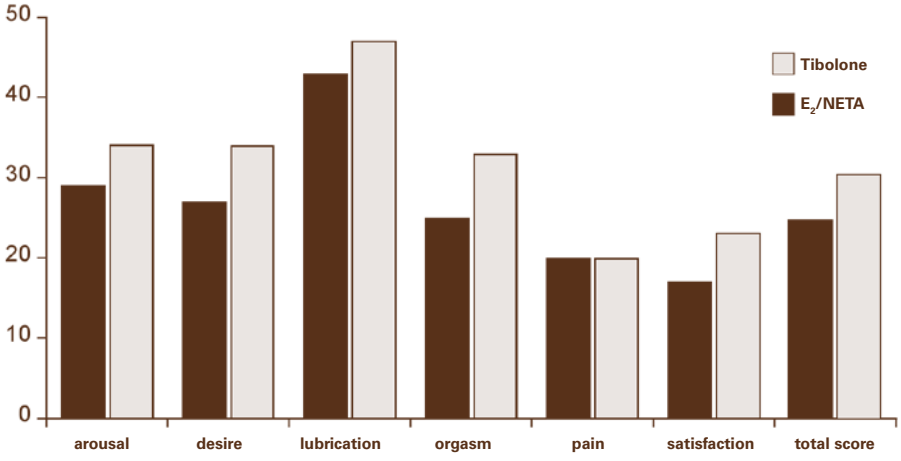


Figure 2. Mean change from baseline in % for the separate domain scores of the FSFI by treatment group at week 24 (Intent-to-treat group n=372)



*p=<0.001 from baseline for all seperate domains for both treatments

Table 2A. Change from baseline in the composite score of the FSFI and total score of the FSFI and FSDS and separate domain score of the WHQ at week 24. (Last value under treatment approach)

Intent-to-Treat Analysis							
FSFI-CS[a]	**tibolone**	**(n=)**	**within group**	**E_2/NETA**	**(n=)**	**within group**	**between groups**
Baseline mean	8.2(2.6)	189		8.2 (2.5)	183		
Mean change from baseline	2.5 (3.4)			1.9 (3.7)			
% change from baseline	30%		p<0.001	23%		p<0.001	p=0.065*
FSFI-TS[b]							
Baseline mean	19.6(5.9)			19.4(6.1)			
Mean change from baseline	5.8(7.5)			4.9(8.2)			
% change from baseline	30%		p<0.001	25%		p<0.001	p=0.092*
FSDS							
Baseline mean	23.8(9.5)			23.9(9.9)			
Mean change from baseline	-7.7(9.5)			-7.8(10.1)			
% change from baseline	-32%		p<0.001	-33%		p<0.001	p=0.724*
Sexual domain score WHQ	**tibolone**	**(n=)**	**within group**	**E_2/NETA**	**(n=)**	**within group**	**between groups**
Baseline mean	2.3(0.8)	189		2.3(0.8)	193		
Mean change from baseline	-1.0(1.2)			-0.9(1.0)			
% change from baseline	-43%		p<0.001	-39%		p<0.001	p=0.203*
Per Protocol Analysis							
FSFI-CS[a]	**tibolone**	**(n=)**	**within group**	**E_2/NETA**	**(n=)**	**within group**	**between groups**
Baseline mean	8.2(2.6)	172		8.2 (2.5)	165		
Mean change from baseline	2.6 (3.3)			1.9 (3.5)			
% change from baseline	32%		p<0.001	23%		p<0.001	p=0.036
FSFI-TS[b]							
Baseline mean	19.8(5.5)			19.1(6.1)			
Mean change from baseline	6.1(7.4)			4.9(7.6)			
% change from baseline	31%		p<0.001	26%		p<0.001	p=0.025

a: FSFI-CS: composite subscore of the FSFI (arousal, desire, satisfaction)

b: FSFI-TS: total score FSFI

*: not significant

Table 2B. Change from baseline in the 4-week frequency of various measures of sexual function measured by a daily diary

	tibolone	(n=)	within group	E_2/NETA	(n=)	within group	between groups
Total sexual events		137[c]			143[c]		
Baseline mean	5.7			5.6			
Mean change from baseline	0.66			0.75			
% change from baseline	12%		p=0.06	13%		p=0.02	N.S
Total satisfying sexual events							
Baseline mean	3.3			3.1			
Mean change from baseline	1.44			1.48			
% change from baseline	44%		p<0.001	48%		p<0.001	N.S.
Frequency of sexual thoughts							
Baseline mean	6.1			5.6			
Mean change from baseline	0.33			0.24			
% change from baseline	5%		N.S.	4%		N.S.	N.S.
Frequency of sexual arousal							
Baseline mean	4.6			5.0			
Mean change from baseline	1.08		p<0.01	0.76		N.S.	N.S.
% change from baseline	23%			15%			
Frequency of taking the initiative							
Baseline mean	2.1			2.2			
Mean change from baseline	0.62			0.60			
% change from baseline	30%		p<0.01	27%		p<0.01	N.S.
Frequency of refusing the partner's initiative							
Baseline mean	2.1			2.6			
Mean change from baseline	-0.95			-0.72			
% change from baseline	-45%		p<0.001	-27%		p<0.001	p<0.001

c: Subjects who failed to record the diary on more than 3 days were considered as missing and not included in the analysis.

N.S. = not significant

Table 3. Serum hormone values at baseline and during the study period for tibolone and transdermal E_2/NETA

Hormone reference range [lower limit-upper limit]	Treatment	Baseline	Week 12	Week 24
Free testosterone	tibolone	15.2 (12.5)	18.0 (13.8)	17.0 (10.7)
[<17.4 pmol/L	E_2/NETA	13.1 (7.6)	12.6 (8.8)	12.8 (8.4)
Total testosterone	tibolone	0.8 (0.5)	0.7 (0.4)	0.7 (0.4)
[0.35-2.08 nmol/L]	E_2/NETA	0.8 (0.4)	0.7 (0.4)	0.7 (0.4)
SHBG	tibolone	56.8 (28.0)	30.0 (17.7)	31.1 (18.7)
[19.8-122 nmol/L]	E_2/NETA	59.8 (25.6)	57.7 (25.6)	53.8 (22.6)
DHEAS	tibolone	2.5 (1.6)	2.6 (1.5)	2.6 (1.5)
[0.78-8.66 µmol/L]	E_2/NETA	2.1 (1.4)	2.3 (1.4)	2.1 (1.4)
Estradiol	tibolone	68.8 (102.1)	63.8 (38.2)	59.3(25.6)
[<145.4 pmo/L]	E_2/NETA	58.7 (36.8)	161.8(151.9)	127.0(107.1)

Reference range is given in S.I. units.

Conversion factor to ng/dL for free T= 0.029 ; conversion factor to ng/dL for total T=29.41; conversion factor to pg/mL for E_2 = 0.27; conversion factor µg/dL for DHEAS =38.46.

Table 4. Summary of adverse events by treatment group

Adverse event	Tibolone n=199		E_2/NETA patch n=201	
Any adverse event	122	(61%)	113	(56%)
Serious adverse event	6	(3%)	3	(1.5%)
Drug related adverse event	54	(27%)	69	(34%)
Drug related SAE	1†		1	
Withdrawals due to (S)AE	23	(12%)	41	(20%)
Specific Adverse Events:				
Breast signs/symptoms*	7	(3.5 %)	23[a]	(11%)
Vaginal haemorrhage	0	(0%)	22[b]	(11%)

Data between brackets are given as percentages. a: p<0.01 in favour of tibolone b: p<0.001 in favour of tibolone †: SAE resulting in death *: including breast pain and breast tenderness

Women's Health Questionnaire

At baseline, 32% of the women in the E_2/NETA group and 28% of the women in the tibolone group reported to be satisfied with their current sexual relationship, whereas at week 24 this number increased to 56% for E_2/NETA treated women and 58% for the tibolone treated women being satisfied with their sexual relationship.

Both therapies were associated with improvements of all of the WHQ domains. At week 24 clinically relevant changes from baseline (based on relevant difference between post-and pre-menopausal normative values) were seen for the following domains: somatic symptoms (normative change=0.06; tibolone 0.063, E_2/NETA 0.05), sexual behaviour (normative change= 0.18; tibolone 0.32, E_2/NETA 0.30), vasomotor symptoms (normative change=0.20, tibolone 0.33, E_2/NETA 0.49), sleep problems (normative change=0.12; tibolone 0.14, E_2/NETA 0.15). For the menstrual symptom domain, a statistically significant worsening from baseline was seen in the E_2/NETA group when compared to the tibolone group.

Effects on serum hormones

Mean baseline serum concentrations of FSH, E_2, total T, free T, SHBG and DHEAS were comparable in both treatment groups. Tibolone was associated with significant reduction in mean SHBG levels ($p=0.001$) and increase in free T levels ($p<0.001$); both of these effects were statistically significantly different from those of E_2/NETA. (Table 3)

Adverse Events and discontinuation

The overall incidence of adverse events was comparable between the tibolone and E_2/NETA groups. No androgenic side effects have been reported. A higher percentage of subjects in the E_2/NETA group than in the tibolone group discontinued the trial due to an adverse event (20.4 % vs. 11.6%; $p<0.001$); this was largely a result of a greater incidence of discontinuations in the E_2/NETA group due specific reproductive system adverse events including vaginal haemorrhage and breast disorders (10.0% vs. 1.0%). Seven women (4 in the tibolone group and 3 in the E_2/NETA group) discontinued the trial due to perceived lack of efficacy.

Serious adverse events were experienced by 9 subjects during the in-treatment period, of which 2 (one in each group) were considered to be related to trial medication according to the investigator. One woman assigned to tibolone experienced a cerebral haemorrhage and died two days after the event. In the E_2/NETA group, one woman experienced a hypertensive crisis (hospitalisation with a blood pressure of 188/156 mmHg and faintness) but recovered after ceasing the trial medication (Table 4).

Discussion

This study was undertaken to evaluate the efficacy of tibolone on various measures of sexual function in naturally menopausal women identified with FSD (including arousal and/or desire disorders and personal distress). Our findings indicate a trend for a greater improvement in sexual function with tibolone reflected in a greater increase in the combined score of the domains of sexual desire, arousal and satisfaction, as well as in the total score of the FSFI when compared with transdermal E_2/NETA. The mean frequency of total sexual events in both treatment groups did not change over the study period, however the frequency of satisfactory sexual events increased from 3.3 to 4.7 per 28 days in the tibolone group and from 3.1 to 4.6 per 28 days in the E_2/NETA group. No statistically significant difference was observed between the groups. Overall, women in both groups felt more satisfied with their sexual relationship at the end of treatment, as assessed by both the satisfaction domain of the FSFI and the WHQ. Moreover, women reported less sexuality-related personal distress: after 24 weeks of treatment the FSDS mean scores were reduced from 24 at baseline to around 15 for both groups, which is the cut off level used to discriminate between a sexually functional and sexually dysfunctional status.[13]

Addressing women's sexual dysfunctions is complex and currently in a state of transition.[22] In view of current definitions of disorder, entry criteria for any study on women's sexual dysfunction would most profitably include women who do not have "sexually satisfying events" – or only marginally satisfying events despite willingness to be active.[23]

The frequency of satisfying sexual events was not selected as the primary efficacy endpoint as no normal data concerning sexual frequency were available for this population. Neither was information available about what would be considered a clinically relevant increase in the event rate. In the testosterone-patch trials, the satisfying sexual event rate increased from 3 to 4 per 28 days in the placebo group and from 3 to 5 in the active treatment group. The difference of 1 between the treatment groups is considered to be clinically relevant.[24,25]

In this study, the effect size of the increase in satisfying sexual events was slightly smaller than that reported for the active treatment group in the recently published testosterone-patch studies, although it was larger than that reported for the placebo arm in the same studies.[26-29] In the testosterone patch studies at least 80% of the women used oral E+P formulations, which may have influenced the greater difference between the active treatment group (testosterone and oral E+P) and the placebo group (oral E+P), thus contributing to the statistically significant difference between the groups.

Similar results to those obtained in our trial were reported by Davis et.al. with no statistically significant difference in the frequency of satisfactory sexual events between the testosterone-treated women and the women who were treated with transdermal oestradiol.[30]

The statistically significant improvement in the sexual behaviour domain of the WHQ includes mainly sexual relationship-related items. The improvement in this domain

was not only statistically significant in both groups, but also clinically relevant, when compared to values for healthy (non-FSD) pre-menopausal women.[17] The number of women discontinuing the study due to adverse events is lower to what is commonly seen in HRT trials[31,32] however it was significantly higher in the E_2/NETA group than in the tibolone group mostly due to the vaginal bleeding events.

Oestrogens are a prerequisite for maintaining a healthy vaginal tissue and are reported to improve sexual function in healthy (non-FSD) postmenopausal women.[33,34]The change from baseline in the efficacy parameters in both treatment groups might also be (at least partially) the result of restoring oestrogen levels, as we did not stratify for previous HRT use. The greater increase in FSFI scores in the tibolone-treated women could be explained by the reduction in SHBG and the larger increase in serum free T levels compared with E_2/NETA-treated women.

There are several strengths to this study. We did not exclusively include women from specialised centres and/or after structured interviews to diagnose FSD. This resulted in the inclusion of a broad and heterogeneous FSD population as would be generally seen by primary care physicians or gynaecologists, thus making our findings relevant to general clinical practice. In addition, to avoid the potential worsening of sexual function that may occur with an increase in SHBG, and hence lowered bioavailable testosterone as occurs with oral oestrogen therapy, we used non oral E therapy as a comparator. Also of note, in consideration of the belief that in most middle-aged women "spontaneous" sexual desire might be absent we evaluated initial desire and arousal and separately, the frequency of refusing the partner's initiative as a secondary outcome.[35]

Study limitations include not incorporating a placebo arm, such that the improvements seen in both groups may be partially due to a placebo effect. However, this was not possible for trial integrity reasons: the treatment allocation of the trial could have been un-blinded due to the different properties of tibolone and transdermal E_2/NETA compared to placebo. The efficacy of the two active drugs in relieving climacteric symptoms (particularly vasomotor symptoms and vaginal dryness) combined with the higher incidence of vaginal bleeding in the active treated women, would have resulted in unblinding of a substantial number of subjects in this trial. The major limitation is that the trial was not sufficiently powered to analyse the individual FSFI domains or the significance of rare (serious) adverse events.

Nevertheless, clinical experience with tibolone is extensive and numerous clinical trials have investigated various safety aspects in postmenopausal women.[2,5,36]

For many postmenopausal women, a decrease in sexual interest and desire is part of the menopausal symptom complex.[37,38]Theoretically, a combination of a non-oral oestrogen with testosterone would appear to be an optimal treatment. However, the Endocrine Society recently published clinical practice guidelines for androgen therapy in women (www.endo-society.org) recommend against the use of testosterone as a generalised treatment for sexual disorders in women because of the absence of sufficient safety data and clear methods to establish the correct indication, as well as uncertainties about the dosing regimen.[39] Nevertheless, sufficient data are available to support a step-wise and individualised approach for women suffering from menopausal symptoms and sexual problems.[40,41] In addition to sexual counselling, if vaginal dryness and dyspareunia are

the most prominent complaints, topical oestrogens may be a useful treatment option.[42] If a diminished sexual interest and desire are the main complaints, a systemic pharmaceutical treatment may support sexual counselling therapy. Transdermal E+P (E only for hysterectomised women) or tibolone might be the first line treatment option followed by transdermal E+P and a transdermal androgen. Women should be informed about the potential risks and benefits of the various treatment options.

In conclusion, both treatments in this study resulted in a significant improvement in sexuality scores for the FSFI, a significant reduction in female sexual distress and a greater frequency of satisfying sexual events when compared with baseline. This study supports our hypothesis that tibolone is more likely to restore sexual function, including desire, sexual interest and satisfaction, than transdermal E+P and had a better tolerability profile.

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CHAPTER 9

Tolerability aspects of tibolone versus transdermal E_2/NETA treatment in postmenopausal women with FSD: results of a randomized controlled trial

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Manuscript submitted

Abstract

Objectives: To compare the incidence of vaginal spotting/bleeding events and breast pain between tibolone 2.5 mg and continuous combined transdermal E_2/NETA 50 µg/140 µg after 24 weeks of treatment.

Methods: A double-blind, double-dummy, randomized, controlled trial was performed and assessments were performed at baseline, week 12 and 24. Bleeding/spotting events were recorded in a daily diary. Breast signs and symptoms were collected as adverse events.

Results: A total of 403 women (mean age 56 years) were randomized. Bleeding/spotting events during weeks 1-12 with tibolone and E_2/NETA were 16% and 56%, respectively ($p<0.001$). The corresponding percentages during weeks 13-24 were 12% and 51%, respectively ($p<0.001$). E_2/NETA was significantly more likely than tibolone to be associated with vaginal hemorrhage (11% vs. 0%; $p<0.001$) and breast signs and symptoms (11% vs. 4%; $p=0.015$). Early discontinuations resulting from adverse events were significantly more common in the E_2/NETA group than in the tibolone group (20% vs. 12%), primarily related to withdrawal due to vaginal hemorrhage (8% vs. 0%).

Conclusions: Tibolone has a significantly better tolerability profile than transdermal E_2/NETA as measured by vaginal bleeding, breast pain and treatment continuation.

Introduction

There is growing interest in studies investigating the effects of pharmaceutical intervention therapies on decreased sexual desire and interest in postmenopausal women.[1,2] Tibolone, registered in Europe for the treatment of menopausal symptoms, has shown positive effects on various domains of sexual functioning over and above its documented effects on climacteric symptoms in otherwise healthy postmenopausal women.[3,4] The effects of tibolone are explained by its combined estrogenic and androgenic activity.[5] These androgenic effects have been attributed to the intrinsic capacity of the Δ4-isomer to activate the androgen receptor and to the reduction in sex hormone binding globulin (SHBG), and hence the increased bioavailable testosterone, seen with tibolone therapy.[6,7] Due to its selective tissue estrogenic activity regulation, tibolone is associated with a high amenorrhea rate.[8-11] The lack of endometrial stimulation is a result of inhibition of the sulphatase enzyme, together with the formation of the progestogenic/androgenic Δ4 metabolite. Similar tissue-specific mechanisms inhibit the formation of active estrogens in the breast[12,13] resulting in fewer breast side effects, such as breast pain and increased mammographic density, in women treated with tibolone when compared to continuous combined hormone therapy (HT).[9,10,14]

Continuous combined estrogen plus progestogen avoids the return of the regular monthly bleeding seen with sequential regimens, although it causes more irregular bleeding particularly during the first few months of use.[15] The transdermal route has the advantage of providing more constant plasma concentrations of estradiol and minimizes some of the metabolic adverse effects experienced with oral treatment, such as liver-mediated increases in clotting factors.[16] In addition, transdermal formulations, in contrast to oral estrogen plus progestogen, do not increase SHBG and hence reduce bioavailable testosterone, which might benefit sexual function in postmenopausal women who report sexual problems as part of their menopausal symptom complex.[17,18] The primary efficacy parameter of the study, the effect on sexual functioning, has recently been reported elsewhere.[19]

The primary safety objective in the current study, which was conducted in healthy postmenopausal women with female sexual dysfunction (FSD), was to compare the vaginal bleeding pattern of tibolone with that of continuous combined transdermal estradiol (E_2)/norethisterone acetate (NETA). Adverse effects involving the breast were also compared between the two treatments.

Methods

A 24-week double-blind, double-dummy, randomized, controlled trial was conducted between June 2004 and November 2005 at 29 centres in eight European countries, Australia and the United States in women identified with FSD associated with sexuality related personal distress. Women were required to be healthy, aged between 48-68 years, have undergone a natural menopause, have an intact uterus, have a normal mammogram and cervical smear, have a body mass index of 19-32 kg/m^2, to be in an

established sexual relationship with a sexually functional partner, and to have no other condition or be taking any medication that could have an impact on sexual function. Women were excluded if they had experienced any abnormal uterine bleeding after the menopause, had a double-layer endometrial thickness of >4 mm as assessed by transvaginal ultrasonography, had had major gynecological surgery in the preceding 3 months, had uncontrolled blood pressure, or a history or presence of any malignancy, a suspicious breast lump, mammographic abnormality, cardiovascular or cerebrovascular disease, thromboembolic events, liver, gallbladder or renal disease, severe psychiatric illness, epilepsy or classical migraine headaches. Previous successful use of testosterone, dehydroepiandrosterone, tibolone and progestogen injectable therapy or estrogen plus progestogen depot preparations was allowed with an appropriate washout period. Oral or transdermal estrogen plus progestogen therapy was allowed prior to randomization at the baseline visit. The study was performed in accordance with the Declaration of Helsinki (2000 edition) and the protocol was approved by the Independent Ethics Committee/Institutional Review Board of each study center. All women eligible for the study provided written informed consent.

Treatments

Following a 4-week pre-treatment period, the women were randomized in a 1:1 ratio using a computerized automatic Interactive Voice Response System to receive either E_2 50 µg/NETA 140 µg in the form of a transdermal patch (Estalis®; Novartis, Switzerland) twice weekly or 2.5 mg tibolone (Livial®; Organon, The Netherlands) as a once daily tablet for 24 weeks. Blindness was maintained by use of a once daily placebo tablet or a twice weekly placebo patch. The treatment assignment was stored electronically, and these data were used to allocate future subjects in order to keep any imbalances between treatment groups to a minimum. This information was distributed to the blinded site pharmacist who dispensed the study medications. All investigators, study site personnel and subjects remained blinded until after database lock.

Assessments

Assessments were performed at screening, baseline and weeks 12 and 24 of treatment. Bleeding/spotting events were recorded in a daily diary that was distributed at screening and collected at each visit. The women were asked to record days with "no bleeding", "spotting" (vaginal blood loss requiring no or only one pad/tampon/day) or "bleeding" (vaginal blood loss requiring two or more pads/tampons/day). A bleeding/spotting episode was defined as more than one consecutive day of uninterrupted bleeding and/or spotting separated by at least one day without bleeding/spotting.

Adverse events were documented throughout the study by questioning or examining the women. Events were categorized using the Medical Dictionary for Regulatory Activities coding dictionary (MedDRA). Information on the occurrence of breast pain/tenderness was derived from the adverse events; breast pain and breast tenderness were both coded as 'breast signs and symptoms'.

Statistical analyses

Assuming vaginal bleeding rates of 15% and 50% during weeks 13-24 for tibolone and E_2/NETA, respectively, 78 subjects (39 per group) would have an 80% power to detect such treatment differences between the two groups using a continuity-corrected Chi-square test at a 2-sided 0.05 α level.

The primary safety objective of this trial was to compare the vaginal bleeding rate between the two treatment groups during week 13-24 and was performed using the intent-to-treat (ITT) approach including all women having at least one post-baseline assessment. The bleeding/spotting rates were determined as the percentage of women experiencing at least one bleeding/spotting event per 12-week period (i.e. weeks 1-12 and weeks 13-24). Women were included in the period analysis provided they had received treatment for the entire 84 days and had no more than 10 days of missing values. In cases where 'no bleeding' and 'bleeding and/or spotting' were recorded on the same day, the variable was set to 'missing' for that day. In cases where 'bleeding' and 'spotting' were recorded on the same day, the variable was set to 'bleeding'.

The secondary safety objective was to compare differences in breast side effects between the two treatment groups; analyses were performed using the Fisher exact test.

Post hoc explorative statistical (subgroup) analyses were performed on the women who experienced spotting/bleeding events. The cumulative bleeding/spotting incidence was assessed using Kaplan Meier and the Log Rank test. Analyses using the Wilcoxon rank sum test were performed on the number of bleeding/spotting days, the number of bleeding/spotting episodes and the mean length of bleeding/spotting episodes. The Wilcoxon two sample test was used to analyze the time to the first day of bleeding. All tests were performed two sided with a significance level of 5%.

Results

A total of 403 women were randomized to treatment (201 to tibolone and 202 to E_2/NETA), of whom two in the tibolone group and one in the E_2/NETA group did not receive any study medication. The subject disposition is shown in Figure 1. The baseline characteristics of the participants were comparable in the two groups and are shown in Table 1. The ITT group consisted of 372 women (189 in the tibolone and 183 in the E_2/NETA group). The 24-week treatment period was completed by 293women (153 on tibolone and 140 on E_2/NETA). The main reason for discontinuation was adverse events, which were significantly more common in the E_2/NETA group than in the tibolone group (20.4% vs. 11.6%; $p<0.001$). Overall compliance with treatment was 98% in both groups.

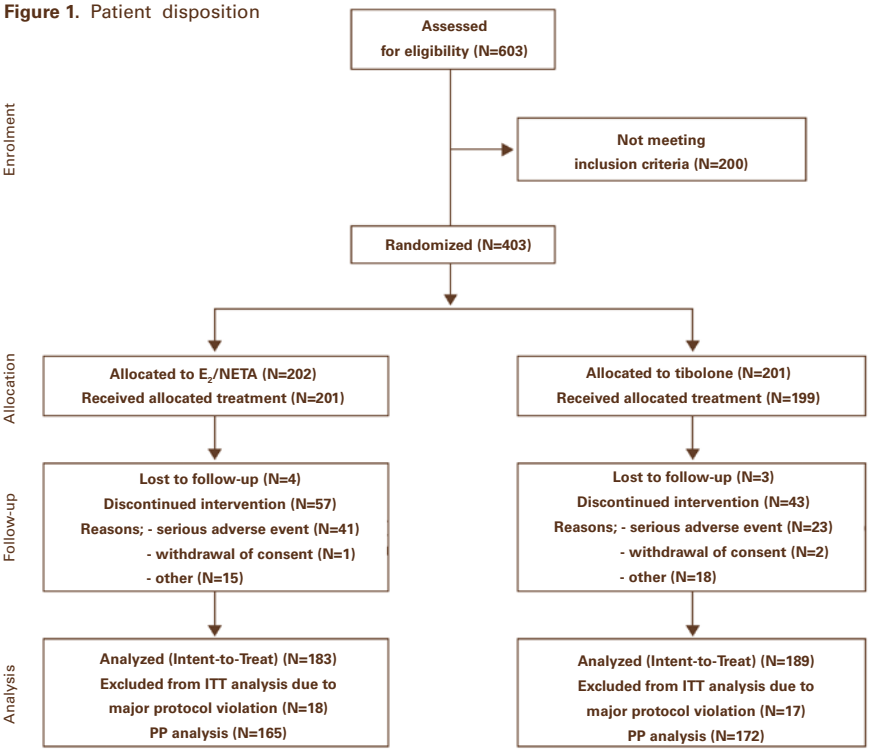
Vaginal bleeding

The percentages of women reporting vaginal bleeding/spotting are shown in Figure 2. In both periods, women on tibolone experienced statistically significantly less bleeding/spotting compared with transdermal E_2/NETA. During weeks 1-12, the bleeding/spotting incidence was 16% vs. 56% ($p<0.001$) for tibolone and E_2/NETA, respectively, and during

Table 1. Baseline demographic characteristics: All-Subjects-Treated group

	Tibolone (N=199)	E_2/NETA (N=201)
	Mean ± SD	**Mean ± SD**
Age (years)	55.8 ± 4.3	55.8 ± 4.4
Height (cm)	164.1 ± 6.3	163.5 ± 6.9
Weight (kg)	67.5 ± 9.5	66.2 ± 9.9
Body mass index (kg/m^2)	25 ± 3.3	24.7 ± 3.3
Percentage subjects with E+P use	55%	48%

Figure 1. Patient disposition



weeks 13-24, 12% vs. 51% (p<0.001) for tibolone and E_2/NETA, respectively. At the end of the study, 24% of women given tibolone had experienced at least one bleeding/spotting day compared with 72% of those given E_2/NETA (p<0.001) (Figure 3). Analysis of bleeding and spotting separately showed that the majority of women experiencing bleeding/spotting events in the tibolone group had spotting only (Figure 2). Thus, during weeks 1-12, only 5% of women experienced at least one day of bleeding with tibolone compared with 29% who experienced bleeding with E_2/NETA. During weeks 13-24, very few women in the tibolone group experienced either bleeding or spotting, whilst in the E_2/NETA group, 32% experienced at least one day of bleeding and 58% at least one day of spotting.

The mean number of bleeding/spotting days and bleeding/spotting episodes was also significantly lower in the tibolone group when compared with the E_2/NETA group (p<0.05) during both weeks 1-12 and weeks 13-24. The duration of bleeding/spotting episodes, however, did not differ significantly between the two groups (Table 2). Amongst women who experienced bleeding/spotting episodes during weeks 1-12, there were a mean of 2.4 episodes that lasted a mean of 3.7 days in the tibolone group compared with 3.2 episodes lasting 4.6 days in the E_2/NETA group. The corresponding values during weeks 13-24 were a mean of 2.2 episodes lasting a mean of 4.9 days in the tibolone group and a mean of 3.9 episodes lasting 4.4 days in the E_2/NETA group.

In general, the percentage of women experiencing bleeding/spotting was significantly greater in the 48-54 years age group than in the group aged 55-61 years (p=0.026); there were no significant differences between the 55-61 and 62-69 year age groups. No statistically significant contribution of years since menopause or previous HT use could be assessed for the percentage of women with bleeding/spotting.

Vaginal hemorrhage was reported as an adverse event by 11% of women treated with E_2/NETA compared with none of those given tibolone (p<0.001). The higher overall incidence of premature discontinuations in the E_2/NETA group than in the tibolone group (20% vs. 12%) was primarily related to withdrawal due to vaginal hemorrhage (8 vs. 0%).

Breast signs and symptoms

The overall incidence of breast signs and symptoms was significantly greater in the E_2/NETA group than in the tibolone group (11% vs. 4%; p=0.015). Breast pain and breast tenderness each accounted for the premature withdrawal of one woman in the E_2/NETA group and one woman in the tibolone group.

(Serious) Adverse Events

The overall incidence of adverse events was comparable between the tibolone and E_2/NETA groups and have been published previously.[19]

Serious adverse events were experienced by 9 subjects during the in-treatment period, of which 2 (one in each group) were considered to be related to trial medication according to the investigator. One woman assigned to tibolone experienced a cerebral haemorrhage and died two days after the event. In the E_2/NETA group, one woman experienced a hypertensive crisis (hospitalisation with a blood pressure of 188/156 mmHg and faintness) but recovered after ceasing the trial medication.

Table 2. Number of bleeding/spotting days, number of bleeding/spotting episodes and length of bleeding/spotting episodes per 12 week period: ITT group

	Tibolone (N=189)		E2/NETA (N=183)		
	n	Mean ± SD	n	Mean ± SD	P-value[a]
Bleeding/spotting days					
Week 1-12	29	8.9 ± 9.7	91	14.4 ± 12.8	0.013
Week 13-24	13	10.2 ± 10.5	46	17.9 ± 12.5	0.022
Bleeding/spotting episodes					
Week 1-12	29	2.4 ± 2.6	91	3.2 ± 1.8	<0.001
Week 13-24	13	2.2 ± 1.7	45	3.9 ± 2.1	0.006
Length of bleeding/spotting episodes (days)					
Week 1-12	29	3.7 ± 2.2	91	4.6 ± 4.3	0.390
Week 13-24	13	4.9 ± 3.4	45	4.4 ± 2.6	0.723

[a]Wilcoxon rank sum test

Figure 2. Spotting and bleeding incidence per treatment group per 12 week period: period 1 (week 1-12) and period 2 (week 13-24) ITT group

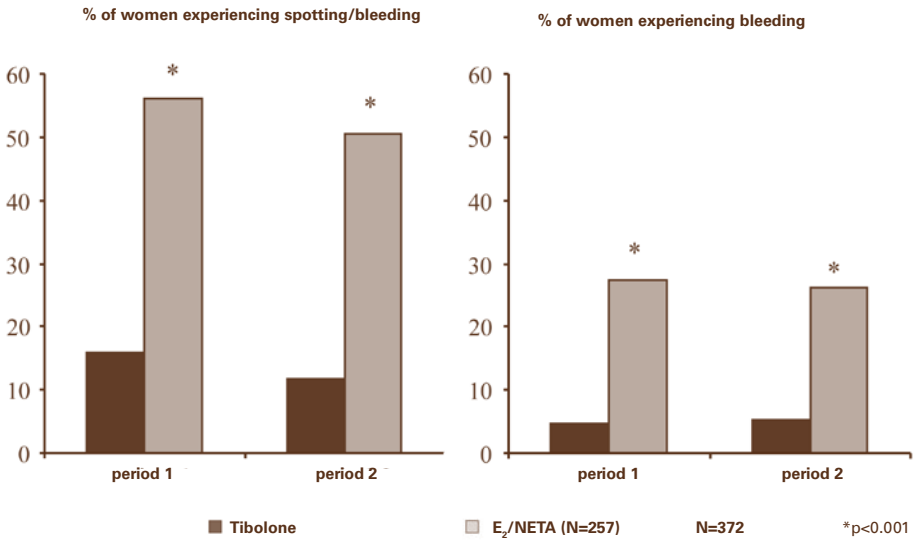
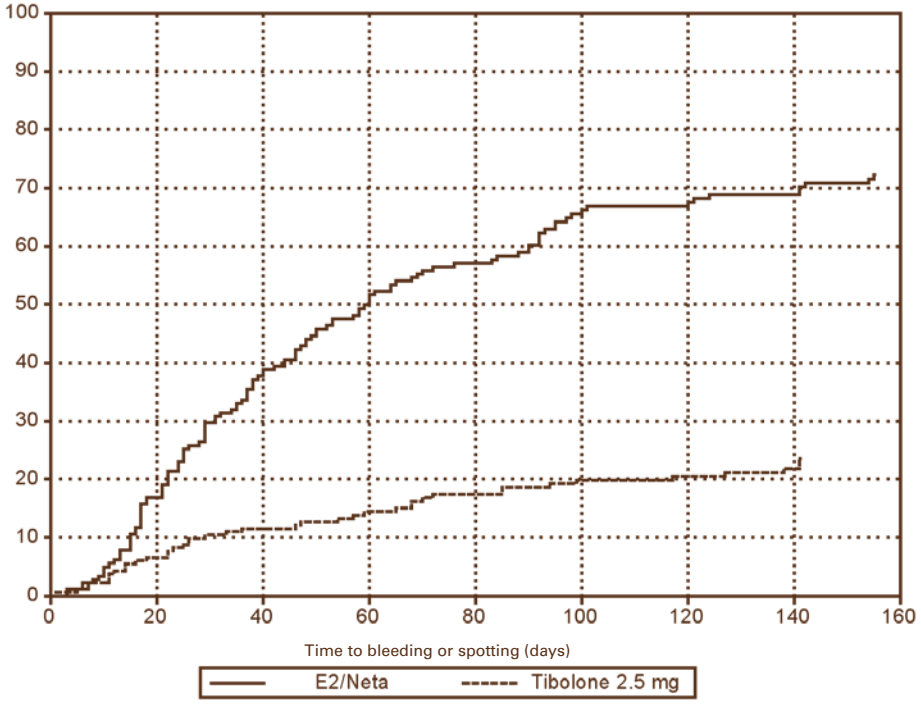


Figure 3. Cumulative spotting and/or bleeding incidence in women treated with tibolone or transdermal E_2/NETA for 24 weeks: ITT group



p-value from logrank test: <.001

Discussion

Previous studies have shown that both tibolone and transdermal E_2 50 µg/NETA 140 µg are associated with good overall amenorrhea rates, with some breakthrough bleeding occurring in the first 3 to 6 months of treatment.[8-11,20,21] However, this is the first double-blind study to directly compare the bleeding profiles of the two treatments during the first 6 months of use. The results showed that tibolone had a better vaginal bleeding profile than transdermal E_2/NETA, with a significantly lower incidence of bleeding/spotting events and a lower mean number of bleeding/spotting days and bleeding/spotting episodes. These differences were apparent during both the first 3 months of use and months 3-6. The majority of women experiencing bleeding/spotting events during the first 3 months in the tibolone group had spotting only, with very few experiencing bleeding; during months 3-6, very few women experienced either bleeding or spotting. In contrast, more than half of the women experiencing bleeding/spotting with E_2/NETA had at least one day of bleeding during both the first 3 months and months

3-6. As might be expected from these findings, the incidence of vaginal hemorrhage reported as an adverse event was significantly higher with E_2/NETA than with tibolone.

Although this is the first comparison between tibolone and transdermal E_2/NETA, several previous double-blind studies have compared the vaginal bleeding profile of tibolone with that of oral continuous combined E_2/NETA. In a 48-week study involving 437 postmenopausal women, tibolone was associated with significantly ($p<0.0001$) fewer overall bleeding/spotting episodes and a significantly ($p<0.0001$) lower discontinuation rate due to vaginal bleeding when compared with 2 mg E_2/1 mg NETA (Kliogest®).[10] These findings were confirmed in another 48-week study conducted in 572 postmenopausal women in which tibolone showed benefits over 1mg E_2/0.5 mg NETA (Activelle®) with regard to the mean bleeding/spotting rate in all four 3-monthly periods and the incidence of vaginal hemorrhage reported as an adverse event.[22]

There are a number of reasons that might account for the better vaginal bleeding profile of tibolone compared with that of E_2/NETA, including the tissue-selective mechanism of action of tibolone and the potential imbalance in angiogenesis modulators caused by NETA that can result in irregular vaginal bleeding.[23] Irrespective of the reasons, however, the clinical consequence of a favorable bleeding profile, particularly over the first few months of treatment, is likely to be good compliance with treatment. Indeed, in the current study, early discontinuations due to adverse events were significantly more common with E_2/NETA than with tibolone, mainly because of withdrawals for vaginal hemorrhage.

Another contributor to poor compliance is breast pain or tenderness, which can cause anxiety as well as discomfort.[24] Women treated with tibolone in the current study were significantly less likely to report breast signs and symptoms than those treated with transdermal E_2/NETA. A higher incidence of breast pain, and withdrawals due to breast pain, has previously been reported with oral continuous combined E_2/NETA than with tibolone.[9,10] Although a recent comparison has indicated that transdermal E_2 50 µg/NETA 140 µg is associated with significantly less breast tenderness than oral continuous combined E_2 2 mg/NETA 1 mg, it appears that it is still more than observed with tibolone.[25] Whether a hormonal treatment is efficacious for the individual woman is dependent on the combined efficacy and safety/tolerability profile.

Women who also report having experienced reduced sexual desire and interest around the time of menopause might benefit from treatments which preserve or increase free testosterone availability for the tissues, such as both tibolone and transdermal E_2/NETA formulations.[26] The way in which irregular vaginal bleeding may influence sexual activity remains to be investigated in this group of women.

In conclusion, tibolone has a significantly better tolerability profile than transdermal E_2/NETA as measured by vaginal bleeding and breast pain, and is associated with better treatment continuation.

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CHAPTER 10

Pharmacotherapy for Female Sexual Dysfunction: explorative analyses of a randomized controlled trial

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Abstract

Introduction: The results of the LISA (Livial Intervention Study in sexuAl dysfunction) have shown that tibolone significantly improves certain aspects of female sexual function in postmenopausal women when compared to transdermal E_2/NETA. As female sexual function is influenced by many factors, an explorative analysis of the LISA data was performed especially since the nature of female sexual dysfunction trials makes the outcome of intervention trials susceptible to bias.

Aim: To gain insight as to which confounders may have influenced the LISA study results and how to interpret the data.

Main outcome measure: Five outcome measures were explored in more detail: whether the study population was well-defined; whether a placebo effect could have significantly influenced the study results; whether the questionnaires administered are applicable in different countries; the consistency of the treatment effect; identification of confounding factors for the outcomes of the Female Sexual Distress Scale (FSDS) and Female Sexual Function Index (FSFI) questionnaires.

Methods: We evaluated data obtained from the FSFI, the FSDS and the Women's Health Questionnaire (WHQ). Analyses concerning the screening and baseline data set were performed on all women screened and all women randomized respectively. Analyses concerning the post-baseline data were performed on the ITT group, using the last observation carried forward approach.

Results: The study population was well defined and reflected a true FSD population. A small but significant placebo effect was seen during the run-in phase of the trial ($p<0.001$) and might have ruled out a significant placebo effect during the active treatment part of the trial. Systematic differences between mean total scores of the FSFI questionnaire between continents exist ($p=0.003$). The consistency of the treatment effect was moderate to good at week 24 (Somer's D coefficient 0.50). The FSDS and FSFI baseline scores are significantly influenced by only a few factors such as age and years since menopause, the greatest factor being the country of origin.

Conclusion: A careful exploration of possible confounders for the LISA trial efficacy outcomes resulted in maintenance of the initial conclusion that tibolone consistently improves sexual function over and above its ability to improve climacteric symptoms when compared to transdermal E_2/NETA in women identified with FSD.

Introduction

The field of sexual medicine has progressed substantially in recent years, both scientifically and clinically and although the study of Female Sexual Dysfunction (FSD) has lagged behind research into male sexual health, it is receiving increasing attention.[1] A major challenge in this field has been that the definition of FSD has been evaluated and revised parallel to the conduct of large randomized controlled intervention studies.[2] As a consequence, for study outcomes to be applicable to daily practice, the results should be evaluated in view of both the past and present insights into FSD. The most commonly reported sexual problems in postmenopausal women relate to sexual desire and interest, pleasure and global satisfaction. It has been proposed that each of these sexual problems present different diagnoses and should be researched and treated differently. However, for most women they are part of a continuum of the sexual experience, and are inextricably related.[3-5] The inclusion and exclusion criteria for recruitment to the large randomized controlled trials (RCT) of pharmacological agents for FSD indicate acknowledgement of the multi-factorial nature of FSD. Nevertheless, the complexity of the female sexual response and the strong impact of contextual factors, make the interpretation of outcomes challenging as well as the measurement of a real treatment effect. Particularly this is true for trials in which the effects of estrogen + progestagen (E+P) combinations are investigated, as the overall beneficial effects of hormonal treatment on mood and general well being impact on sexual function.

In most pharmaceutical intervention studies, the efficacy is measured by validated patient reported outcome instruments.[6-8] It is uncertain whether these instruments are applicable trans-culturally, as in large multi-centered trials, and what exactly is measured when women cannot relate to specific questions.

The LISA (Livial Intervention study in SexuAl dysfunction) study investigating the effects of tibolone versus transdermal E_2/NETA in naturally menopausal women with FSD has been published.[9] Tibolone significantly improved various, but not all, aspects of sexual function when compared to transdermal E_2/NETA. The trial included two active treatment arms (and no placebo group) which resulted in a small difference in effect size between the two groups which did not reach statistical significance in the Intent-to-Treat (ITT) analysis whereas it did in the Per-Protocol (PP) analysis. As the trial was sufficiently powered, this might have been a result of factors other than the intervention, which, due to the nature of the study, could impact on the study outcomes.

The aim of the present study was to gain further insight into the confounders that may have influenced the LISA study results and whether these may have influenced data interpretation. Five outcomes were of interest to us. Firstly, FSD was defined by qualitative criteria accepted at the time the study was designed. Thus women were eligible if they reported that prior to menopause their sex life was satisfying but that since they had experienced a decline in satisfaction with sexual activity and had a FSDS of 15 or more.[10] Subsequently a cut-off score below which women are considered likely to have FSD has been validated for the FSFI.[11] Thus we were interested in the number of participants who would have been eligible with this new definition. We also wished to determine whether the findings for the efficacy endpoints could be explained by

"other-than-intervention"- factors influencing sexual function, also known as 'the Hawthorne effect". [12] Furthermore, as approximately half of the participants did not use HT prior to being randomized, we wanted to explore whether improved general well-being due to HT could account for the improvement in sexual function and whether any other baseline characteristics predicted response to therapy. As the study was conducted in several different countries with significant cultural differences, we were interested whether there were differences in the baseline data for the questionnaires administered by country. We also had the opportunity to explore the stability of the treatment effect by comparing the pattern of responses to the FSFI and the sexual wellbeing domain of the Women's Health Questionnaire (WHQ).

Methods

Subjects

The design and conduct of this 24 weeks prospective randomized controlled study of the efficacy and tolerability of tibolone versus transdermal E_2/NETA for the treatment of FSD in naturally postmenopausal women has been described in detail elsewhere.[9] 9 For the present study the analyses concerning the screening and baseline data set were performed on all women screened and all women randomized respectively. Analyses concerning the post-baseline data were performed on the ITT group, using the last observation carried forward approach. This report pertains to data obtained from the Female Sexual Function Index (FSFI), the Female Sexual Distress Scale (FSDS) and the Women's Health Questionnaire (WHQ). Tests were performed at a two sided significance level of 5%.

Outcome measure 1: Adequacy of the definition of the study population

The screening FSFI scores for women included in the trial were compared with the recently proposed cut-off level of the FSFI (a total score of 26.55) to assess whether the subjects were correctly included (Frequency table, no statistical test performed).

Outcome measure 2: Hawthorne effect

Screening FSFI and FSDS data were compared with baseline FSFI and FSDS data to examine whether there was a shift in mean total scores reflecting an improvement in sexual function without any trial medication. (Wilcoxon rank sum test).

An analysis was then performed for the group of women who did not use HT prior to the trial to assess whether the measured efficacy on sexual function for the total trial population could be explained by the general HT effect on wellbeing in this group (stratified Wilcoxon rank sum test).

Outcome measure 3: Consistency of the questionnaires for different cultures

During the trial women in several European centers made remarks about the sexuality questionnaires asking items not completely covering their feelings about their sexual problems. Especially women in Sweden reported that they could not identify themselves

as having feelings of guilt, inferiority and inadequateness related to sexuality, separate items being part of the FSDS 12-item scale.
Based on these thoughts, we estimated that women of different continents might have been comparable personally distressed but may have interpreted and scored the FSDS differently due to linguistic interpretation problems.
The following hypotheses were tested:

1. The screening FSDS mean total scores differ between continents assuming a lower (i.e. better) mean FSDS score at screening for Europe (and specifically Sweden).
2. The screening FSFI mean total scores are comparable between the three continents Europe, Australia and the U.S.A.
3. Differences exist per continent in the correlation between screening FSDS scores and baseline FSDS scores and no differences exist per continent in the correlation between screening FSFI scores and baseline FSFI scores.
4. No differences at a continent (country) level exist in the shift (Δ) in the mean FSDS scores between screening and baseline and the shift (Δ) in mean FSFI scores between screening and baseline.

The Kruskall Wallis test was applied to test systematic differences between the sexuality questionnaire scores per continent. In addition, correlation analyses for the total study population and per continent (Australia, Europe and USA) and Sweden separately were performed.

Outcome measure 4: Stability of the treatment effect

To assess whether the treatment effect was consistent if measured by two different questions frequency distributions of scores on WHQ question 31 and FSFI question 15, which each ask about sexual relationship satisfaction, at baseline and at week 24 respectively were calculated. The association between both questions is reflected in Somers'D coefficient (range -1.0—1.0).

Outcome measure 5: confounding factors influencing efficacy outcomes

To explore whether the efficacy outcomes have been influenced by confounders we investigated the distribution of treatment discontinuations per treatment group and treatment continuation in spite of (drug) related adverse events using the Fisher exact test. The Influence of the partner's health, body mass index (BMI), β-blocker use, previous HT use, age, years since menopause and continent on the baseline total scores of the FSFI and FSDS and separate domain scores of the FSFI.
was tested by the Kruskal-Wallis test. In the analyses we classified women by age: (48-54; 55-61; 62-69), continent (Australia, Europe (excluding Sweden), Sweden, USA), years since menopause (0-<2, 2-<5, 5-<15,>15); BMI (<27 or ≥ 27) β-blocker use (yes or no), previous HT use (yes or no), pa (yes or no, defined as use of medication influencing sexuality and/or severe illness influencing sexual function).

Results

1. Subjects: definition of the population

In total 603 women completed the screening visit and entered the 4 week run-in phase prior to baseline (randomization) visit and 403 women were randomized to treatment. In Australia 63 women were randomized, in Europe 244 women were randomized (Sweden n=77) and in the U.S.A. 65 women were randomized.

The main reasons for not being randomized to study treatment included concomitant illness influencing sexuality, specified contra-indications for HT, a CES-D depression scale score >16 (indicating depression), a FSDS score < 15 (no presence of sexuality related distress), no established sexual relationship or relationship problems.

Baseline demographics were comparable between the two randomized groups. Prior HT use was reported by 52% of the women randomized to tibolone and by 45% of the women randomized to E_2/NETA. At baseline 91% of the women randomized to E_2/NETA and 89% of the women randomized to tibolone reported to have lost interest in sexual activity according to their answers on the WHQ. 66% of the women in the E_2/NETA group were not satisfied with their current sexual relationship at study entry versus 71% of the women in the tibolone group.

96.7% of the women included based on the FSDS screening score ≥15 had a total FSFI screening score below 26.55, the recently proposed cut-off score for the FSFI, discriminating between a clinical and a non-clinical population.

Eight women with a FSDS score < 15 at screening were erroneously included in the trial. However, a post-hoc analysis revealed that seven of these women were at risk for having FSD according to their screening scores at the FSFI.

2. Treatment effect versus Hawthorne effect and general HT effect

Figures 1a and 1b. show histograms of the screening and baseline values of the total scores of the FSDS and FSFI. From screening to baseline a significant increase in mean total FSFI score of 1.2 was seen for the total trial population ($p<0.001$). For the FSDS, a significant mean total score decrease of -1.6 was seen from screening to baseline for the total trial population ($p<0.001$). At baseline 50 women (13.5%) had a FSDS score of <15 (i.e. not personally distressed by sexual function) of which 8 women scored the FSFI ≥ 26.55 (not at risk for having FSD). In total 29 women (13.5%) at baseline had a FSFI score ≥ 26.55.

No effect of HT could be demonstrated for the change from baseline (CFB) total FSFI scores or any of the FSFI domains in each of the two treatment groups.

3. Consistency of the sexuality questionnaires for different continents

1. Mean total FSDS (±SD) scores at screening and baseline were 24.4 (7.84) and 23.4 (8.96) for Europe (excluding Sweden), 25.2 (7.41) and 22.4 (9.49) for Sweden, 26.3 (7.42) and 25.4 (9.37) for the U.S.A. and 26.9 (8.79) and 24.7 (8.65) for Australia respectively. No systematic differences in the mean screening scores or the mean baseline scores between continents could be demonstrated for the FSDS at the 5% significance level.

2. Mean total FSFI (±SD) scores at screening and baseline were 17.8 (6.4) and 18.7 (6.2) for Europe (excluding Sweden), 17.8 (5.8) and 20.0 (5.3) for Sweden, 16.5 (5.3) and 17.6 (5.6) for the U.S.A. and 16.2 (6.4) and 17.0 (5.9) for Australia.
   A trend for systematic differences in the mean screening FSFI total score between continents was seen and a systematic difference for the mean baseline FSFI total score was demonstrated at the 5 % significance level. See table 1.
3. Table 2. shows correlation coefficients for the FSDS and FSFI at screening and baseline. For the total trial population, a good correlation (r = 0.61) was found between FSDS screening and FSDS baseline values as well as for FSFI screening and FSFI baseline values (r= 0.69). No significant differences in correlation coefficients per continent could be assessed. The correlation between the screening FSDS and baseline FSDS was lowest for the Swedish population when compared to the total trial population or the different continents but was not significantly different at the 5% significance level.
4. Table 3A. shows the change from screening to baseline (Δ) of the mean FSDS scores per continent. Although the difference between screen and baseline FSDS scores was largest for Sweden and smallest for Europe, no significant differences between continents and Sweden separately could be assessed.
   Table 3B shows the change from screening to baseline (Δ) of the mean FSFI total score, composite score and separate domain scores. Significant differences could be demonstrated between continents for the total score, the composite sub score and the domain satisfaction. Sweden showed the greatest difference in the (positive) change from screening to baseline FSFI for the total score, composite sub score and the domain satisfaction.

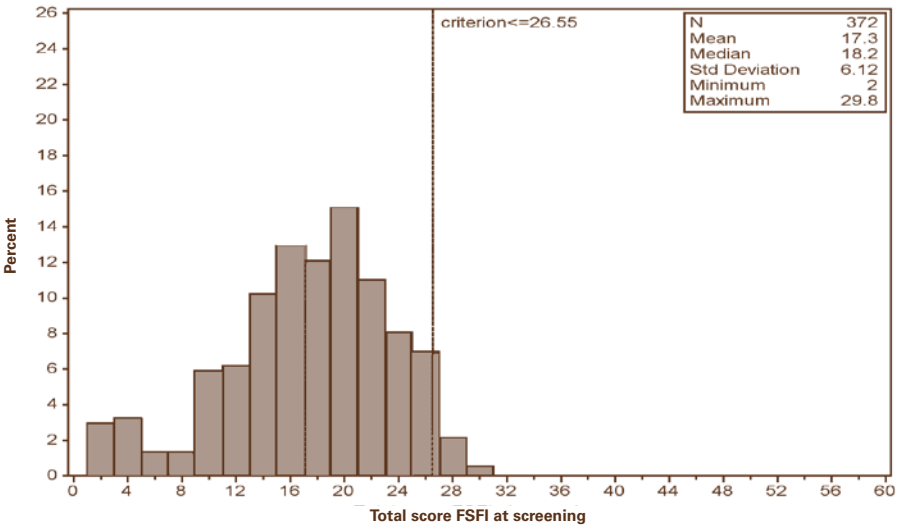
4. Stability of the treatment effect

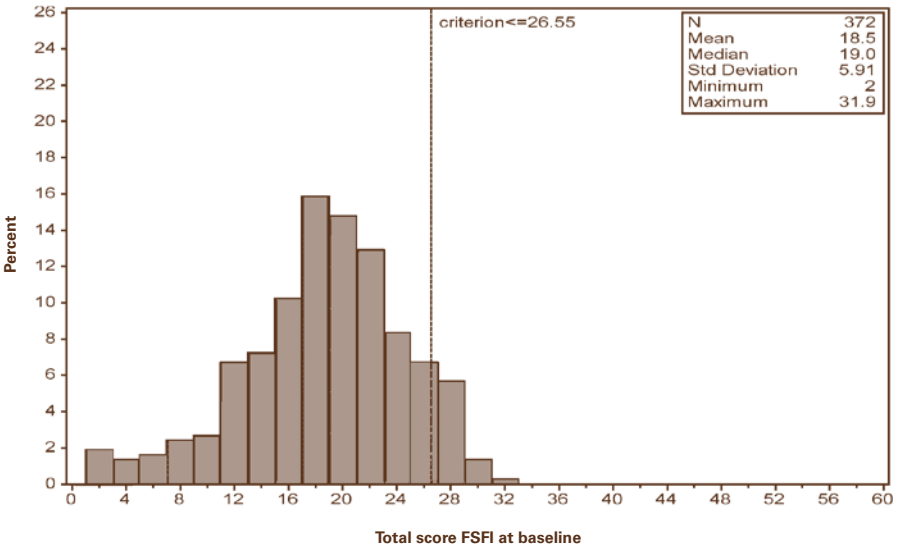
Tables 4a and 4b show the frequency distribution of scores on WHQ question 31 and FSFI question 15 at baseline and at week 24 respectively The association between both questions is reflected in Somers'D coefficient (range -1.0—1.0). In spite of both questions measuring the satisfaction of the sexual relationship, the Somers'D coefficient is weak at baseline (mean 0.31) and moderate (mean 0.50) at week 24. At week 24 the satisfaction with the sexual relationship improved as both the "general feeling" (WHQ item I am satisfied with my current sexual relationship) and the time-dependent feeling (FSFI item: over the past 4 weeks I have been satisfied with my sexual relationship) improved in terms the higher frequency of positive answers and the higher association found between the two answers.

5. Confounding factors on efficacy measurement

During the first three months, 16% of the women treated with tibolone and 56% of the women treated with E_2/NETA experienced irregular vaginal bleeding and/or spotting events ($p<0.001$). Early treatment discontinuations due to (S)AE's was statistically significantly higher in the transdermal E_2/NETA group than in the tibolone group (20.4% vs. 11.6% respectively $p=0.01$). The majority of women discontinued treatment due to a (serious) adverse event, primary due to severe vaginal bleeding events occurring in 11%

Figure 1A. Histograms of FSFI scores at screening and baseline, Intent-ToTreat-group

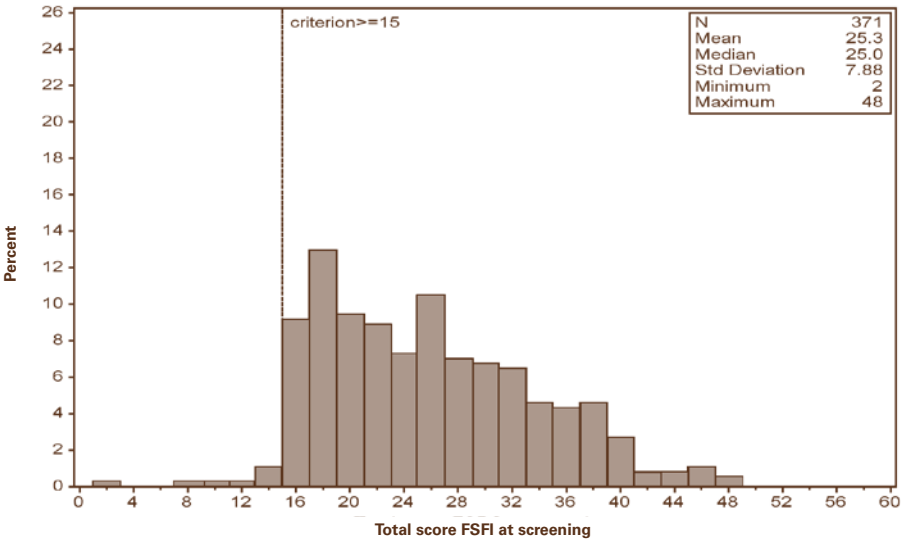


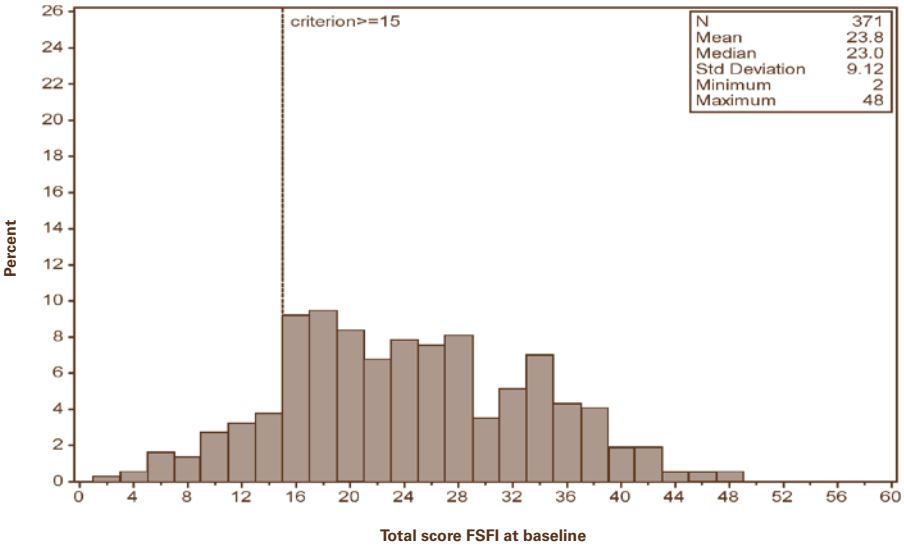


of the women in the E_2/NETA group and in 0% of the women in the tibolone group ($p<0.001$). 4 women in the tibolone group and 3 women in the E_2/NETA group discontinued treatment due to perceived lack of efficacy. Treatment continuations in spite of adverse events were comparable between groups: 36 women in the tibolone group and 32 women in the E_2/NETA group continued treatment in spite of drug related adverse events.

The role of influencing factors on the FSDS and FSFI total score and separate domain scores at baseline is shown in Table 1.

Figure 1B. Histograms of FSDS scores at screening and baseline, Intent-To-Treat-group





From Table 1. it can be seen that age has a significant effect on the domains desire and satisfaction and years since menopause have a significant effect on the FSFI domains arousal, desire and satisfaction whereby a trend was seen that how older the age category and how longer the time since menopause the better the scores on the FSFI.
The factor continent has a significant effect on all domains of the FSFI whereby Europe and especially Sweden give higher median (mean) scores for all domains compared to Australia and USA.
No factors could be determined which influenced the FSDS baseline scores.

Table 1. P-values Kruskall-Wallis test for influencing factors on the total FSDS score and total and separate domain FSFI scores at baseline, Intent-To-Treat-group

	Age[1]	Years since meno-pause[2]	Partner's health (Y/N) (medication or disease)	Previous HT use (Y/N)	BMI kg/m (<27/>=27)	βeta-blockers use (Y/N)	Continent[3]	Continent[3] at screening
FSDS total score	0.420	0.134	0.990	0.599	0.803	0.319	0.164	0.118
FSFI total score	0.330	0.177	0.937	0.697	0.720	0.921	**0.003**	0.077
Arousal	0.504	**0.047**	0.661	0.931	0.083	0.481	**0.008**	**0.009**
Desire	**0.010**	**0.003**	0.932	0.950	0.515	0.778	**0.012**	0.097
lubrication	0.447	0.426	0.706	0.342	0.946	0.195	**0.014**	0.239
Orgasm	0.802	0.232	0.887	0.505	0.196	0.404	0.065	0.123
Pain	0.694	0.872	0.531	0.888	0.094	0.520	**0.032**	0.092
Satisfaction	**0.004**	**0.046**	0.597	0.612	0.865	0.197	**0.041**	0.284

[1]age categories: 1)48-54 2)55-61 3)62-69, [2]years since menopause categories: 1)0-<2 2)2-<5 3)5-<15 4)>=15, [3]continent: Australia, USA, Europe (excluding Sweden), Sweden. Bold p<0.05 (statistical significant at 5%)

Table 2. Spearman Rank Correlation coefficients between total scores of the FSDS and FSFI at screening and baseline, Intent-To-Treat-group

Total trial population	FSDS total score at baseline	FSFI total score at screening
FSDS total score at screening	0.61	
FSFI total score at baseline		0.69
By continent:		
U.S.A		
FSDS total score at screening	0.69	
FSFI total score at baseline		0.76
Australia		
FSDS total score at screening	0.64	
FSFI total score at baseline		0.70
Europe (excluding Sweden)		
FSDS total score at screening	0.59	
FSFI total score at baseline		0.67
Sweden		
FSDS total score at screening	0.49	
FSFI total score at baseline		0.64

Table 3A. Summary scores for continent on the FSDS delta score delta= baseline minus screening (intent-to-treat group)

Continent	N	Mean	Median
AUSTRALIA	61	1.69	2.0
EUROPE EXCLUDING SWEDEN	162	0.93	0.0
SWEDEN	76	2.80	2.0
USA	64	1.03	2.0

Kruskal-Wallis test for continent on the FSDS delta score: p=0.451

Table 3B. Summary scores for continent on the FSFI delta score delta= baseline minus screening w(intent-to-treat group)

Domain	Continent	N	Mean	Median
Arousal	AUSTRALIA	63	0.15	0.0
	EUROPE EXCLUDING SWEDEN	167	0.16	0.0
	SWEDEN	77	0.40	0.3
	USA	65	0.19	0.3
Composite subscore (p=0.005)	AUSTRALIA	63	**0.23**	**0.1**
	EUROPE EXCLUDING SWEDEN	167	**0.13**	**-0.3**
	SWEDEN	77	**1.09**	**0.9**
	USA	65	**0.33**	**0.3**
Desire	AUSTRALIA	63	-0.09	0.0
	EUROPE EXCLUDING SWEDEN	167	-0.07	0.0
	SWEDEN	77	0.07	0.0
	USA	65	0.10	0.0
Lubrication	AUSTRALIA	62	0.08	0.0
	EUROPE EXCLUDING SWEDEN	167	0.16	0.0
	SWEDEN	77	0.39	0.3
	USA	65	0.09	0.0
Orgasm	AUSTRALIA	61	0.33	0.0
	EUROPE EXCLUDING SWEDEN	167	0.22	0.0
	SWEDEN	77	0.53	0.4
	USA	65	0.45	0.4
Pain	AUSTRALIA	63	0.15	0.0
	EUROPE EXCLUDING SWEDEN	167	0.36	0.0
	SWEDEN	77	0.26	0.0
	USA	65	0.26	0.0
Satisfaction (p=0.003)	AUSTRALIA	62	**0.20**	**0.0**
	EUROPE EXCLUDING SWEDEN	165	**0.04**	**0.0**
	SWEDEN	77	**0.62**	**0.4**
	USA	65	**0.04**	**0.0**
Total score (p=0.045)	AUSTRALIA	61	**0.83**	**0.4**
	EUROPE EXCLUDING SWEDEN	165	**0.87**	**0.0**
	SWEDEN	77	**2.27**	**2.0**
	USA	65	**1.12**	**1.3**

Systematic differences between continents was tested with the Kruskal Wallis test at the 5% level

Table 4A. Frequency (%) distribution of scores on the WHQ item 31 and the FSFI item 15 baseline, Intent-To-Treat group

Questionnaire	WHQ: Item 31, I am satisfied with my current sexual relationship								Total N
	1) No not at all		2) No not much		3) Yes sometimes		4) Yes definitely		
	n	%	n	%	n	%	n	%	
FSFI: Item 15, Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?									
1) Very dissatisfied	52	14.4	9	2.5	2	0.6	2	0.6	65
2) Moderately dissatisfied	49	13.6	30	8.3	17	4.7	8	2.2	104
3) About equally satisfied and dissatisfied	27	7.5	20	5.6	15	4.2	8	2.2	70
4) Moderately satisfied	28	7.8	22	6.1	31	8.6	4	1.1	85
5) Very satisfied	8	2.2	6	1.7	14	3.9	8	2.2	36
Total	164		87		79		30		360

Somers D, row independent, column dependent (95% cl): 0.28 (0.21, 0.36)
Somers D, column independent, row dependent (95% cl): 0.33 (0.24, 0.41)
Spearman rank correlation coefficient (95% cl): 0.36 (0.26, 0.45)

Table 4B. Frequency (%) distribution of scores on the WHQ item 31 and the FSFI item 15 LVUT, Intent-To-Treat group

Questionnaire	WHQ: Item 31, I am satisfied with my current sexual relationship								Total N
	1) No not at all		2) No not much		3) Yes sometimes		4) Yes definitely		
	n	%	n	%	n	%	n	%	
FSFI: Item 15, Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?									
1) Very dissatisfied	28	7.8	6	1.7	5	1.4	3	0.8	42
2) Moderately dissatisfied	22	6.1	17	4.7	15	4.2	4	1.1	58
3) About equally satisfied and dissatisfied	13	3.6	19	5.3	24	6.7	2	0.6	58
4) Moderately satisfied	11	3.1	17	4.7	53	14.8	28	7.8	109
5) Very satisfied	5	1.4	9	2.5	18	5.0	59	16.5	91
Total	79		68		115		96		358

Somers D, row independent, column dependent (95% cl): 0.49 (0.42, 0.56)
Somers D, column independent, row dependent (95% cl): 0.51 (0.44, 0.59)
Spearman rank correlation coefficient (95% cl): 0.58 (0.49, 0.66)

Discussion

Although no standard screening tool to determine FSD was available at the time of our study design and in spite of women being recruited in non-specialized centers it seems that the population randomized to our study can be regarded as a true FSD population given the large percentage (96.7%) of women who both had an FSDS score above the cut-off level of 15 and a FSFI score below the cut-off level of 26.55. This supports the recently proposed idea to use a structured diagnostic method (SDM) including a couple of questionnaires to determine FSD for research purposes.[13] It also opens possibilities for non-specialized centers to participate in a FSD study which likely results in an inclusion of a more heterogeneous patient population making the results of such a trial more applicable to daily practice.

Women included in any FSD trial are susceptible to a placebo effect as the process of being in such a study, with attention given to sexual parameters in itself leads to improvements in sexual function. Therefore, the changes in sexuality questionnaire scores from screening to baseline, described as the "Hawthorne effect", were analyzed. Both the FSFI and the FSDS showed statistically significant improvements during this 4 week run in period (from screening to baseline). In this way a part of the placebo effect might have been ruled out as women at baseline were already used to the questionnaires. The mean increase of 1.2 at the FSFI and the mean decrease of 1.6 at the FSDS between screening and baseline is probably not clinically relevant. However, it might give an estimation of the placebo effect in such a trial.

As we had expected, women in Europe and specifically Sweden scored lowest at the FSDS, however the difference when compared to the other countries did not reach statistical significance. Similar to the above finding women in Europe and Sweden scored systematically different (higher) at the FSFI screening questionnaire when compared to the other continents which was against our expectations that the FSFI screen scores per continent would not differ. The factor continent was the most prominent influencing factor for the outcomes of the baseline FSFI as not only the total score but also various domain scores were significantly affected by this cultural factor. The correlation between the screening and baseline FSDS for the total trial population was fair as was the correlation between the screening and baseline FSFI. Differences existed at a continent level but no systematic differences could be determined.

No differences per continent existed for Δ FSDS between screening and baseline. However, contrary to what we had expected, systematic differences per continent existed for the Δ FSFI between screening and baseline. Sweden showed the largest shift from screening to baseline for both the FSDS and the FSFI total score when compared to the combined European countries or the U.S.A or Australia. One explanation for this phenomenon might be that women in Sweden are more susceptible to a "Hawthorne" effect. Another possible explanation could be that women in Sweden had difficulties understanding the FSDS and FSFI and completed the questionnaires at screening in a way to make sure to be included in the trial. At baseline 50 women of the total trial population had a FSDS score ≥ 15 (not personally distressed) of which 30 women were from the Swedish group.

Various other factors influenced the baseline FSFI domain scores such as age and years since menopause. Interestingly, the age factor and years since menopause influenced the domains which were selected as primary endpoint for the LISA trial (composite score of the domains desire, arousal and satisfaction) which underscores the relative important contribution of age and menopause to these aspects of sexuality. It might also be that these aspects are hormone dependent and that for this reason both treatment groups in the LISA trial experienced an improvement in sexual function.

Partner's health and/or partner's medication use did not significantly influence the baseline FSFI total scores. However, partner's health did negatively influence the treatment effect as has been shown in the primary result paper of this study whereby a statistically significant difference was only found in the PP analysis after excluding women with a diseased partner and/or not being compliant to the trial medication. Previous HT use did not influence the baseline FSFI scores neither did it influence the treatment effect of the trial medication. This is curious as in many previous reports, HT improves sexual function by improving general quality of life factors such as vasomotor symptoms and sleep. In the recently published INTIMATE-NM-1 study, in which naturally menopausal women were randomized to 300 µg testosterone plus estrogen and progestagen (E+P) or to placebo plus E+P a 3 month "run-in" phase was required in which all women were treated with E+P in order to rule out the general HT effect on sexual function.[14] Although the results of our study indicate that there is no difference in effect size between women who have used HT prior to the trial and women who did not, it seems reasonable to require this 3 month HT run in phase for future trials investigating pharmacologic intervention for hypoactive sexual desire disorder (HSDD) viewing the large treatment effect of the active control arm (E_2/NETA) in our study which cannot be totally explained by the administration route (transdermal) as the SHBG and subsequently free T levels in the E_2/NETA arm remained pretty constant from baseline to week 24.[9]

The influence of β-blocker use at the baseline FSDS and FSFI scores could not be determined although the number of women using β-blockers was small (n=17). Due to the small numbers, a statistical analysis for the β-blocker effect on CFB FSFI scores was not performed.

Women 0-2 years beyond menopause and women more than 15 years past menopause had higher scores as the FSFI and separate domain scores when compared to women between 2 and 15 years past menopause. A possible explanation for this is that the women shortly past natural menopause do not experience yet the "late-onset" effects of estrogen deficiency such as vaginal atrophy and possibly still do have "sufficient" circulating androgens for their personal feelings of sexual well being as androgen levels decrease gradually, independent of the onset of menopause and moreover, are reserve pool for estrogens which can be aromatized from androgen precursors in the peripheral tissues. The difference in scores was not so clear in the different age groups. Women in age group 48-54 and 55-61 had relatively comparable FSFI separate domain scores. The older age group (62-69) had somewhat higher scores at the arousal, desire and satisfaction domain whereby it must been noted that this group was relatively small and that selection bias can have taken place. Younger postmenopausal women have bigger problems with sexual function compared to older postmenopausal women. The sexual

satisfaction domain was inversely correlated with age and years past menopause, a finding which has been reported by other authors as well.[15]
Treatment discontinuation due to irregular vaginal bleeding was significantly higher in the E_2/NETA group. This did not influence the outcome of the primary efficacy analyses on sexual function. The number of women discontinuing treatment due to perceived lack of efficacy was generally low and equally divided over the two groups.
Several cautious conclusions can be drawn from our study results. First, that for future multicenter trials the assessment tools (sexuality questionnaires) must be linguistically and culturally validated to be able not only to compare trial outcomes per country but also make them applicable to multi cultures. It seems that the FSDS is a stable questionnaire less influenced by cultural differences and/or placebo ("Hawthorne") effect possibly due to the conciseness of the questionnaire. The FSFI is susceptible to cultural differences (as reflected in the systematic differences between mean FSFI screening scores per continent) and more susceptible to change over time (either due to a placebo effect or a "Hawthorne" effect) as reflected in the systematic differences per continent of the ΔFSFI between screening and baseline;
second, a large part of the placebo effect and general HT effect can be ruled out if a run in phase of 3 months is used in which all women complete a sexuality questionnaire at the beginning and after 3 months the latter then serving as the screening assessment;
third, an age span of 15-20 years is possibly too wide for sexuality trials viewing the influence of age and years since menopause on various aspects of sexuality. For future trials the authors recommend to include age subgroups of similar size not being broader than 5-10 years;
fourth, the inclusion of a true FSD population is possible in a multicenter trial if a structurized diagnostic method is used combining at least on validated sexuality questionnaire and a sexual distress questionnaire and fifth; that the results of our trial are solid namely that tibolone has a significantly better effect on sexual function in postmenopausal women with FSD than conventional transdermal E_2/NETA as the trial results were not unequally influenced by selection bias, placebo effects, dependency of HT use previous to the trial or an unequal division of early discontinuations over the two study arms due to perceived lack of efficacy.

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INTERPRETATION OF THE RESULTS AND SUMMARY

CHAPTER 11

General Discussion

General discussion

A major challenge in research and clinical management of FSD is that a general accepted sexual response model for women applicable for both preclinical and clinical research is lacking. More specifically, it is unclear which is the role of pharmacotherapy in this response model. This thesis aimed to contribute to the understanding of sexual function after menopause and potential pharmacological treatment options.
In total, 1287 women were randomized to three different clinical trials investigating in total four different pharmacological interventions: tibolone 2.5 and 1.25 mg, raloxifene 10 mg, oral continuous combined E_2 1 mg/NETA 0.5 mg and transdermal continuous combined E_2 50 µg /NETA 140 µg.

The pioneers work: Defining the problem and defining the methodology to perform this thesis

As we were well aware of the controversial role of the pharmaceutical industry, regarded by many as "creating a disease from a normal life event", we first explored the attitude of women towards sexuality after menopause and their needs for therapy (Chapter 4). The majority of women consider sexuality after menopause as important as before menopause and believe they would enjoy life more if their sexual function would improve to previous levels. Their main need is to discuss sexual problems with a health care professional who, preferably actively asks for the presence of sexual problems. Unfortunately, the prevalence of a decreased sexual interest and desire is highly underestimated by physicians and an active discussion is, in many cases, not sought. Only one third of the women is bothered enough by their sexual problems such that they would be open for pharmacotherapy, if this was available. This suggests that in daily practice, when a woman expresses her concern about her sexual problems, she not only merits a careful evaluation of her sexual problem but also needs to be offered sexual counselling/education and an advice about possible pharmacological treatment options.

Second, we reviewed previously published pharmacological intervention studies and determined what the short comings of these studies were in order to design an intervention trial which was, at that moment in time, the most appropriate study design. (Chapter 5).
The studies presented in Chapter 6 and Chapter 7 were part of two separate ongoing trials. None of these trials required the women to have a "minimal set" of climacteric symptoms (including the presence of sexual problems). The raloxifene versus tibolone trial (Chapter 6) was designed with the primary aim to measure the effects of both treatments on bone mineral density. The low dose oral E_2/NETA (Activelle®) trial (Chapter 7) was designed to compare tolerability aspects, such as irregular vaginal bleeding. Thus the effects of the drugs employed in these studies may represent a true effect on sexual function as women were not "hindered" by certain expectations to improve their sexual function with these drugs. Also, the indirect effects on climacteric symptom relief and the subsequent improvements in sexual function might be, at least

partially, ruled out by including women who experienced, if at all, only mild climacteric symptoms.
Chapter 6 shows that in an elderly patient population, tibolone confers some beneficial effects on sexual function. However, no differences between the two treatments could be assessed which was against our expectations especially since the two drugs differ considerably in their oestrogenic-action profile. One explanation for this is, that the trial was underpowered to measure significant differences between groups due to the small number of women providing data for the McCoy sexuality questionnaire which was approximately one third of the total trial population at baseline. This is because many women in this study did not consider the issue applicable to them. In addition, a considerable number of women from this small group discontinued completing the McCoy sexuality questionnaire over the 2 year duration of the trial which resulted in a dilution of the effect size as for the statistical analysis an imputed case analysis was employed to account for missing data (of note: at week 52, one year before trial completion, the difference between groups for the McCoy total score approached statistical significance (p=0.10) as did the orgasm domain (p=0.093) and lubrication domain (p=0.037) in favour of the tibolone group. Obviously, it is also possible that women of older age and/or being longer after menopause do benefit less from tibolone treatment with regard to sexual function, or, would benefit only with the standard-and higher dosage of 2.5 mg.
Chapter 7 represents the first randomized controlled clinical trial of sufficient power showing a significant difference between tibolone and continuous combined oral E_2/NETA on sexual function measured by the total score of the McCoy sexuality questionnaire. Both treatments resulted in a significant increase from baseline in sexual function, an effect which was more pronounced and significantly larger in the tibolone group when compared to the E_2/NETA group. A major limitation of both this trial as well as the trial described in Chapter 6 is that the total score of the McCoy sexuality questionnaire is used as an outcome measure. This questionnaire is no longer regarded as a useful tool to measure sexual function and treatment effect over time as it appears to be a too 'coarse meshed' net to pick up the sensitive features of female sexuality and the small differences made by a pharmacological treatment.

This Thesis

The key components in this thesis are reported in Chapter 8, 9 and 10. The studies presented in these chapters are part of a randomized clinical trial specifically designed to assess the effects of tibolone versus transdermal E_2/NETA in postmenopausal women with FSD. Both tibolone and transdermal E_2/NETA improved various aspects of sexual function measured by the FSFI sub domain scores and total score. The effect was significantly larger in the tibolone group in the per protocol analysis after exclusion of women who had been seriously non-compliant to medication and women who had a partner who, during the trial developed a disease which interfered with sexual function such as prostate carcinoma, myocardial infarction or depression (Chapter 8). Women in the tibolone group experienced significantly less irregular vaginal bleeding when compared to transdermal E_2/NETA which suggests tibolone to become a first line

treatment option for women who in addition to their need for climacteric symptom relief, experience sexual problems (Chapter 9).
A careful exploration of possible confounders for the LISA trial efficacy outcomes (Chapter 10) resulted in maintenance of the initial conclusion that tibolone consistently improves sexual function over and above its ability to improve climacteric symptoms when compared to transdermal E_2/NETA in women identified with FSD. Although a considerable placebo effect can be assumed in trials investigating the effect of pharmacological treatment on FSD it does not seem to have significantly influenced our trial results. A factor of significant influence on the baseline scores of the sexuality questionnaires was the country of origin. We have not investigated whether differences in treatment effect between countries or continents did exist and whether the treatment effect was dependent of certain (cultural) expectations. This remains a topic for future research.

Potential limitations of this work: methodology

1. Lack of a placebo arm

One limitation of this work has been the lack of a placebo arm, such that a partial placebo effect of both treatments on sexuality cannot completely be ruled out. We have, however, tried to address this issue by using a run in phase in which women could get used to the sexuality questionnaires and a sufficient long trial duration (24 weeks). After an initial increase in FSFI scores at week 12 in both treatment groups, a further increase is seen in the tibolone group whereas the scores of the FSFI in the transdermal E_2/NETA group remained pretty constant. If a significant placebo effect would be present, it is likely that for both treatments a regression to the mean would have been seen after this follow up time of 24 weeks.
A study employing a placebo comparator would not test the question whether tibolone has benefits for sexual function over its oestrogenic effects. Therefore, this study was designed with a careful selection of a comparator that would match the oestrogenic and progestogenic activity of tibolone without altering SHBG such that one could evaluate whether tibolone had any further advantage of having an androgenic effect.
Women treated with placebo would continue to experience unchanged climacteric symptoms and vaginal dryness and even women who do not consider themselves "symptomatic" at menopause often feel better in terms of sleep and mood with therapy. A small percentage of women treated with active trial medication would experience vaginal bleeding both issues leading to unblinding the trial.
All recently published testosterone-patch trials were comparative trials against (mostly oral) HRT and not versus non-active placebo for similar reasons. However, as oral HRT increases SHBG levels and herewith decreases endogenous free testosterone levels, these trials were actually measuring the efficacy of an active treatment (testosterone) versus a treatment which is likely worse than a pure placebo with regard to sexual function. The effects of oral oestrogen plus progestagen regimens versus pure placebo on sexual function in women with FSD has, however, never been investigated.

2. Definition of FSD

To date, rare or absent spontaneous desire - desire present at the outset of sexual engagement- is not regarded necessarily dysfunctional. Impairment of response with little arousal or enjoyment such that desire is not accessed or "triggered" at any time during the sexual experience is now the basis of the diagnosis of dysfunction.[1] The FSFI scores are below the cut off level for 'dysfunction' but the instrument (and other current validated instruments) reflect the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. definitions of sexual dysfunction - these definitions themselves being modelled on the human sex response cycles of Masters, Johnson and Kaplan.[2]

So the women in this study may not be diagnosed with dysfunction using 2003 recommended definitions of dysfunction. Nevertheless, they all experienced sexuality related personal distress and the majority of women was not satisfied with their sexual relationship at baseline. So at least women had identified a sexual problem combined with personal distress. Also a diary question about the responsiveness to the sexual partner's initiative was included in our trial, which may reflect better the current definitions of sexual dysfunction.

In view of the current definitions of FSD, entry criteria for any study on women's sexual dysfunction would most profitably include women who do not, or only marginally, have "sexually satisfying events" despite willingness to be active. Such women would experience little subjective or physical arousal, little pleasure and fail to trigger desire during sexual engagement. However, women in this study were having on average three sexually satisfying events per month which increased to four.

The requirement of a minimal frequency of sexual activity for inclusion in a trial investigating FSD results in a selection bias. This has also been shown in Chapter 6 which shows how few, otherwise healthy, elderly postmenopausal women provided data for the McCoy sexuality questionnaire, the main reason being absence of sexual activity.

It is questionable if 3 satisfying sexual events at baseline can be regarded as dysfunctional and also what improvement one can expect from any (pharmacological) intervention.

3. FSFI composite sub-score as primary outcome measurement

No "gold-standard assessment tool" is available how to measure treatment effect in FSD. This topic is continuously being discussed. The selection of the sexual desire, satisfaction and arousal domain of the FSFI was considered valid at the start of the trial because 1. a lack of sexual desire and interest and lack of arousal is the most frequently heard sexual complaint by postmenopausal women so it would be clinically relevant to find a treatment improving these domains and 2. from previous studies we knew that tibolone had beneficial effects on sexual arousal and desire and 3. the domain lubrication was not expected to show any treatment differences between groups as both treatments have similar oestrogenic effects on the vagina. Closely correlated with the lubrication domain is the "pain" domain which we did not select as a primary endpoint for similar reasons as the one mentioned above. The domain orgasm was

considered to be more dependent of "adequate sexual stimulation" than of a woman's sexual function except for arousal, which latter domain is closely correlated with the orgasm domain.
At the time of protocol design, the results of the T-patch trials were not available yet, so it was very difficult to do a power analysis for a primary endpoint of which the normative range was not known (i.e. the frequency of satisfying sexual events).

Future clinical perspective

Pharmacological therapy for Female Sexual Dysfunction: a psychological, medical and social issue

Medical treatment for something complex as female sexual function is not straightforward, especially since it is only recently that women's sexual health is acknowledged within the Western society and health care community. Criticism about the role of pharmacological intervention for FSD include overestimating the prevalence and impact of female sexual disorders and the risk of precipitating sexual inadequacy if women's sexual problems are labelled as dysfunctions.[3-5] Obviously, it is wrong to make a woman feel diseased or defective just because she does not feel a certain way. However, it is just as wrong to discount a woman's distress when she presents with sexual problems and wants to be treated. To assume that women's sexual problems all stem from psychological, relational or cultural factors is not based on evidence and precludes women to access all possible treatment options by assuming that biological treatments are, by definition, inappropriate.
Another important issue to mention is the concern many have regarding the safety of medical treatment, specifically hormones, for FSD. Hopefully, now the dust has settled down from publications such as the Women's Health Initiative[6] and Million Women Study[7], a more balanced and individual approach will be taken regarding the use of hormones especially since the fear of hormones has, apparently, not been generalized to men: testosterone replacement patches and gels for men are easily available and have not been subject to extensive safety reviews by regulating authorities and phosphodiesterase inhibitors type 5 (PDE5-Viagra®) was approved for erectile dysfunction despite concerns about an increased risk of myocardial infarction. In addition, the recreational use of these medications in men without erectile dysfunction is well known. Apparently a double standard is used which may reflect different values placed on the importance of sexual health in women versus men.
Medicine is the art of curing and caring. Sexual problems are not life threatening but life altering. Caring for female sexual health endorses an individual's general health and well-being as is stated in the in 2000 published document by the World Health Organisation entitled "promotion of sexual health." This document of fundamental and universal human rights includes the right to sexual pleasure as sexual pleasure is a source of physical, psychological and spiritual health and well-being.[8]

Classical Hormone Treatment: Oestrogens plus progestagen combinations and tibolone for postmenopausal sexual dysfunction

The studies and analyses included in this thesis indicate that a standard dose of tibolone (2.5 mg) is more likely to restore sexual wellbeing than conventional or transdermal oestrogen/progestin therapy in postmenopausal women, although the beneficial effect of transdermal estrogen plus progestin on sexual function can be expected in women switching from oral to transdermal E+P formulations.

Testosterone for postmenopausal sexual dysfunction

Large RCTs in both surgically menopausal[9-11] and naturally menopausal women[12] for which the frequency of satisfactory sexual events was the primary endpoint, demonstrate that treatment with the transdermal testosterone patch, which delivers 300 microgram of testosterone per day, significantly increased the number of self-reported sexually satisfying events per month when compared with placebo. These studies also demonstrated significant improvements in desire, arousal, responsiveness, orgasm, pleasure and satisfaction.

Safety aspects

The links between postmenopausal oestrogen-progestin use and both breast cancer and cardiovascular disease (including stroke) have created a level of concern regarding any form of hormone use in women.[6] Testosterone has been widely used by women as an unapproved therapy for decades. There is no evidence from studies in premenopausal women or postmenopausal women using systemic oestrogen treated with testosterone for up to 24 months, or studies of women with chronic androgen excess due to polycystic ovarian syndrome, that elevated testosterone levels, even above what is considered physiologically normal, are associated with altered breast cancer risk.[13,14] Primate and human studies suggest that testosterone as well as tibolone may in fact protect the breast from oestrogen induced breast cell proliferation.[15-19] However this is an area of considerable controversy which needs to be addressed in future research.

For women many years past menopause, sufficient safety data about restoring oestrogen or testosterone levels are absent. Recently, tibolone has been reported to increase the risk of stroke in elderly postmenopausal women (mean age 68 years).[20,21] Also the safety of testosterone treatment with regard to the cardiovascular system has not been established in elderly postmenopausal women, neither are sufficient safety data available for long term testosterone treatment.[22]

Therapeutic options

For postmenopausal women (> 1 year past menopause), tibolone where available, should be considered as first line therapy, not only because of its greater effects on sexual function when compared to oestrogen plus progestagen treatment but also because of its favourable tolerability profile. As part of the efficacy of tibolone may reside in the reduction of SHBG and hence increase in free testosterone it may be

that women with very low testosterone levels, such as those who have had a surgical menopause, will benefit less. However there is no clinical data to support this hypothesis. Tibolone is not indicated for use by premenopausal women.
An alternative option, especially for peri-menopausal women where cycle control might be required, or, in women with severe vasomotor symptoms, is to initially change women from oral oestrogen to a (sequential) transdermal therapy as oral oestrogen therapy tends to result in an increase in sex hormone binding globulin (SHBG) and hence lower free testosterone[23] and evaluate after at least 3 months whether this has resulted in an improvement in sexual interest.
Transdermal testosterone patch therapy has only been approved in Europe for women who have undergone surgical menopause, but it is likely that the approval will eventually be extended to naturally menopausal women.

Who to treat

A pragmatic concern is which women are candidates for pharmacotherapy for FSD? To date, no clinically applicable diagnostic algorithm has achieved acceptance. A low serum testosterone level is not predictive of a diagnosis of low libido nor does it predict likelihood of therapeutic response.[24] It is clear that women with complaints of low desire are a heterogeneous population and, as our survey has shown, most women would never consider any treatment as they are not bothered enough by their sexual problems.
The concern of some, that addressing sexual issues would increase the incidence of a sexual dysfunction which needs to be (pharmacologically) treated is not based on evidence. For the majority of women, the identification of a sexual health problem followed by counselling and education would already be sufficient to relieve sexuality related personal distress. This approach is not different from the approach in other non-life threatening medical conditions which affect life quality such as low back pain.
The assessment of the woman presenting with low sexual wellbeing requires a comprehensive clinical evaluation by a professional specialized in sexual problems. If no clearly identifiable cause can be found in an otherwise healthy postmenopausal woman a trial of tibolone therapy should precede initiation of testosterone with/without oestrogen therapy.
Women who have undergone premature ovarian failure or surgical menopause, or who have adrenal insufficiency or hypopituitarism, are known to have loss of androgen production also merit consideration for treatment. The first therapy option in these women would be testosterone.

A social issue

FSD remains a complex, controversial and under-researched clinical issue. Women experiencing FSD have the right to treatment with effective and safe therapeutic options.
There is widespread off-label use by women of testosterone products approved for men, and extensive prescription of compounded testosterone products for women in clinical practice. It is currently easier to purchase testosterone patch (via internet without

prescription) than to have an easy access to individual sexual counselling by health care professionals in a safe and private environment.

An over-sexualized culture, which is a complaint of many, can only be changed if we openly discuss sexual function and its context in a professional way. The pharmaceutical industry at least merits acknowledgement for boosting this discussion.

The future management of female sexual health is a matter of collaboration between health care providers, pharmacists, industry and policy makers. The first step is to listen to women and respect their feelings and experiences.

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CHAPTER 12

Summary

Summary

This thesis was designed to evaluate the effect of hormone therapy (HT) and specifically tibolone on sexual function in postmenopausal women with female sexual dysfunction (FSD).
To be able to answer this general question several considerations were explored before having identified the right angle to perform this project: therefore several sub-research questions were defined:

1. What is the attitude of postmenopausal women and doctors regarding sexuality after menopause?
2. What is the correct research approach in investigating pharmacological intervention for FSD?
3. What is the effect of tibolone, combined oestrogen plus progestagen and raloxifene (a selective oestrogen receptor modulator) on sexual function in postmenopausal women?
4. What is the net androgenic effect of tibolone over and above its oestrogenic effects in postmenopausal women with FSD?

The aim of our study was to contribute to the current knowledge about the role of hormone therapy on female sexual function and to search for pharmacological treatment options which could fit in a multi-dimensional, but also clinically practical approach in the treatment of sexual problems.

Chapter 4

Sexual Well-Being after 50: A European Survey among Women and Physicians

The objective of this study was to describe current women's thoughts about sexuality after menopause in various European countries and to identify current physicians attitudes towards sexuality during and after menopause.
A survey was conducted in 6 European countries interviewing over 3000 menopausal women and 600 doctors who treated menopausal women. The majority of women (67%) reported to experience symptoms affecting sexual well-being including vaginal pain/dryness and/or a reduced sexual interest and desire which negatively influenced their quality of life and the relationship with their partner. To them, the main reason for a reduced sex-life was menopause and growing older. In spite of a high prevalence of sexual problems, many women remained sexually active but experienced less pleasure from sex.
To 61% of the women, sexual activity remained as important as before the menopause and a similar percentage reported that they would enjoy their life more if their sex drive would improve to previous levels. In spite of experiencing a reduced sexual interest and/or desire, the majority of women was satisfied with their sexual relationship.

Vaginal dryness/dyspareunia was not reported as a major factor influencing quality of life or sexuality. Most women with sexual problems had never considered a treatment, as they were not bothered enough by their sexual problem. 35% would consider to take a drug to help solving sexual problems, if this was available. Women felt they were more likely to discuss their sexual problem if the doctor would bring up the subject.
Physicians underestimated the prevalence of a reduced sexual desire and interest in their patients, however, they overestimated the prevalence of vaginal dryness and dyspareunia as a reason for postmenopausal sexual problems. More than one third of the doctors were the opinion that discussing sexual problems is a taboo and also one third reported to find it difficult to discuss sexual health concerns with elderly patients.
Apparently, women and doctors see menopause related sexual problems differently: educating both women and doctors concerning sexuality may remain one of the crucial elements to resolve menopause related sexual problems prior to starting any treatment.

Chapter 5

Female Sexual Satisfaction and Pharmaceutical Intervention: a Critical Review of the Drug Intervention Studies in Female Sexual Dysfunction

This chapter addresses the study of FSD as this is an evolving research area in which a correct research approach has not been fully established due the fact that a new female sexual response model has recently been proposed followed by continuous revisions of the definition of FSD.
The aim of this study was to evaluate the needs in research into intervention in female sexual dysfunction (FSD) by reviewing published randomized controlled pharmaceutical intervention studies. This chapter summarizes the limitations and issues of these studies and the relevance of the outcomes for clinical practice. Unresolved questions were identified and proposals to optimize the design of future studies made.
The main outcome of our review was that a standard methodology for research in this field is lacking especially regarding the population inclusion requirements and tools for the measurement of change in sexual functioning.
In order to be able to measure a treatment effect of the intervention which is clinically meaningful for a woman the following issues need to be resolved prior to initiating new intervention trials in FSD: A universally accepted method for defining the FSD population is needed and as a result a consensus should be reached for appropriate inclusion and exclusion criteria for FSD trials. Similarly main outcome measures appropriate for the evaluation of drug intervention should be defined. Trial endpoints need to reflect clinically relevant outcomes and should be embedded in a bio-psycho-social sexual response model for women.

Chapter 6

Effects of tibolone and raloxifene on health related quality of life and sexual function

This chapter compares the effects of tibolone and raloxifene on health related quality of life, sexuality and vaginal atrophy in elderly, osteopenic but otherwise healthy, postmenopausal women. We performed a two years, prospective, double blind clinical trial in 308 women (mean age 66 years) who were randomized to tibolone or raloxifene.

Health related quality of life was assessed by the Women's Health Questionnaire (WHQ), sexual function by the McCoy Female Sexuality Questionnaire (MFSQ) and vaginal atrophy by assessing the Karyopycnotic Index (KI) and Vaginal Maturation (VM).

Tibolone improved health-related quality of life, with WHQ values approximating those for premenopausal women, whilst women treated with raloxifene showed a trend towards a poorer quality of life. Changes from baseline of a few WHQ domains were significantly larger in favor of the tibolone group when compared to the raloxifene group, particularly the sexual behavior, attractiveness and vasomotor symptoms domains all showed a statistically significant improvement from baseline.

Less than half of the women in the trial provided data for the MFSQ, the main reason being the absence of sexual activity. No difference could be assessed between the tibolone and raloxifene group in mean total score and separate domains scores of the MFSQ, except for the vaginal lubrication domain (p= 0.037). This was also reflected in the VM and KI index which showed an improvement with tibolone, whilst there were no meaningful changes in the raloxifene group.

A post-hoc separate item analysis showed significant differences in favor of the tibolone treated women on a few questions at various time points which included the presence of sexual thoughts and fantasies (p=0.047), feeling aroused/excited (p=0.038) and a decrease in pain during intercourse (p=0.02).

Tibolone and raloxifene were equally well tolerated and no serious adverse events regarding the cerebrovascular and/or cardiovascular system were reported.

This study shows that also in older postmenopausal women, tibolone treatment showed a trend towards an improvement in quality of life and sexuality whereas raloxifene has no added benefits on these aspects.

Chapter 7

Effects of tibolone versus low dose oral E_2/NETA on urogenital complaints, sexuality and quality of life in postmenopausal women: results of a randomized controlled clinical trial

This chapter addresses the effects of tibolone versus oral low dose E_2/NETA (1mg/0.5mg) on sexual function, urogenital complaints and quality of life in postmenopausal women. We performed a 48-week multicenter, randomized, double blind, double dummy, group comparative trial. Several questionnaires were used to measure response to therapy:

the McCoy sexuality questionnaire for sexual function, the Women's Health Questionnaire (WHQ) for health related quality of life and the Urogenital Complaints Scale (LUGCS).
572 postmenopausal women aged 45-65 years were included in this trial. After 48 weeks of treatment, both treatments showed an added benefit to healthy postmenopausal women by improving sexual function, quality of life and urogenital complaints when compared to baseline. Tibolone's beneficial effect on sexual function was, however, more pronounced and particularly present in a subset of women who were identified with sexual problems at baseline. A significantly greater effect of tibolone on the increase in the mean total score of the McCoy sexuality questionnaire (p=0.038 for the total trial population) and the mean score of the McCoy sexual interest domain was shown. In addition, the "satisfaction with the sexual relationship"- domain of the WHQ showed a clinically relevant improvement in the tibolone treated women and not in the E_2/NETA treated women.

Chapter 8

Tibolone and transdermal E_2/NETA for the treatment of Female Sexual Dysfunction in naturally menopausal women: results of a randomized active-controlled trial

This chapter focuses on the effects of tibolone in sexual function over and above its documented ability to relieve climacteric symptoms in postmenopausal women with FSD. In order to make a scientifically justified comparison, we performed a 24 week, randomized, double blind clinical trial with tibolone versus transdermal E_2/NETA as an active comparator.
The primary objective was to assess differences between treatment groups in the change from baseline for the composite sub-score of the arousal, desire and satisfaction domains of the self-reported FSFI (Female Sexual Function Index). Secondary outcomes included the outcomes of the Female Sexual Distress Scale (FSDS) and the frequency of satisfying sexual events (daily diaries).
403 women, mean age 56 were included. In the per-protocol analysis, which consisted out of the women who had been compliant to the trial medication and had a sexual partner who stayed sexually functional during the trial, the increase in FSFI scores was significantly larger in the tibolone group when compared with the E_2/NETA patch group at week 24 (p=0.036 and p=0.025 for the composite sub-score and total FSFI score respectively). This difference could not be assessed in the intent-to-treat analysis. At week 24, the satisfying sexual event rate increased from 3 to 4 times per 28 days (p<0.001 from baseline for both groups), with no difference between groups. The FSDS showed a significant decrease from baseline (p<0.001) which was comparable for both treatment groups. Of importance, a significant reduction in refusal of the "initiative for sexual activity" of the partner was seen in favour of tibolone-treated women when compared with E_2/NETA-treated women (-45% vs. -28%; p<0.001). Tibolone was associated with a significant reduction in mean SHBG levels (p=0.001) and an increase in free T levels (p<0.001); both of these effects were significantly different from those of E_2/NETA. However, no correlation between hormone levels and outcomes regarding sexual

unction could be assessed. The overall incidence of adverse events was generally low and comparable between groups, although a substantially higher percentage of women in the E_2/NETA group discontinued the trial due to irregular vaginal bleeding.
In conclusion, although both treatments resulted in a significant improvement in sexuality scores of the FSFI, a significant reduction in female sexual distress and a greater frequency of satisfying sexual events when compared to baseline, tibolone is more likely to restore sexual function than transdermal E+P and has a better tolerability profile.

Chapter 9

Tolerability aspects of tibolone versus transdermal E_2/NETA treatment in postmenopausal women with FSD: results of a randomized controlled trial

This chapter addresses tolerability aspects of tibolone and transdermal E_2/NETA (50 µg/140µg) with the main outcome measure being the vaginal bleeding event rate. As a part of the randomized, double blind clinical trial with tibolone versus transdermal E_2/NETA, a primary safety objective was included which specifically determined the tolerability profile on the reproductive system in each of the two treatment groups.
Bleeding/spotting events were recorded in a daily diary that was distributed at screening and collected at each follow up visit. The bleeding/spotting rates were determined as the percentage of women experiencing at least one bleeding/spotting event per 12-week period (i.e. weeks 1-12 and weeks 13-24). Women were included in the period analysis provided they had received treatment for the entire 84 days and had no more than 10 days of missing values. In both periods, women on tibolone experienced significantly less bleeding/spotting compared with transdermal E_2/NETA. During weeks 1-12, the bleeding/spotting incidence was 16% vs. 56% ($p<0.001$) for tibolone and E_2/NETA, respectively, and during weeks 13-24, 12% vs. 51% ($p<0.001$) for tibolone and E_2/NETA, respectively. At the end of the study, 24% of women given tibolone had experienced at least one bleeding/spotting day compared with 72% of those given E_2/NETA ($p<0.001$).
The overall incidence of breast signs and symptoms was significantly greater in the E_2/NETA group than in the tibolone group (11% vs. 4%; $p=0.015$). Adverse events besides those affecting the reproductive system were generally low and comparable between treatment groups.
In conclusion, tibolone has a significantly better tolerability profile than transdermal E_2/NETA as measured by the incidence of vaginal bleeding and breast pain, and is associated with a better treatment continuation.

Chapter 10

Pharmacotherapy intervention for Female Sexual Dysfunction: explorative analyses of a randomized controlled trial

This chapter evaluates into more detail the outcome measures of the studies presented in the previous two chapters, since these kind of trials are particularly susceptible to

bias by their nature (human behaviour and pharmacological intervention). The aim of the present study was to gain insight as to which potential confounders may have influenced the LISA study results and how to interpret the data.
Data were obtained from the FSFI, the FSDS and the Women's Health Questionnaire (WHQ) and analyses concerning the screening and baseline data set were performed on all women screened and all women randomized respectively. Analyses concerning the post-baseline data were performed on the ITT group, using the last observation carried forward approach.
The outcomes of our explorative analyses were the following:
The study population was well defined and reflected a true FSD population. A small but significant placebo effect was seen during the run-in phase of the trial ($p<0.001$) and might have ruled out a significant placebo effect during the active treatment part of the trial. Systematic differences between mean total scores of the FSFI questionnaire between continents exist ($p=0.003$). The consistency of the treatment effect was moderate to good at week 24 (Somer's D coefficient 0.50). The FSDS and FSFI baseline scores are significantly influenced by a few factors such as age and years since menopause, the greatest factor being the country of origin.
Nevertheless, the initial conclusion that tibolone consistently improves sexual function over and above its ability to improve climacteric symptoms when compared to transdermal E_2/NETA in women identified with FSD, was maintained.

Chapter 11

General discussion

European middle aged women experience menopause as a process that brings sexual changes able to impair their personal life. However, cultural values and health beliefs influence the perception of sexual changes and the need for treatment. One third of the women would be open for pharmacotherapy to help solving sexual problems if this was available. Counselling and education remains one of the pivotal pillars in a multi-dimensional treatment approach. The (indirect) effect on sexual function of restoring oestrogen levels by hormone treatment, especially transdermal estrogen plus progestagen formulations, is considerable, although elderly postmenopausal women might benefit less.
If pharmacotherapy is indicated, tibolone should be considered the first line therapy option for postmenopausal women with sexual problems/sexual dysfunction as both its direct effects on sexual function as well as its combined tolerability and safety profile is sufficiently established.

CHAPTER 13

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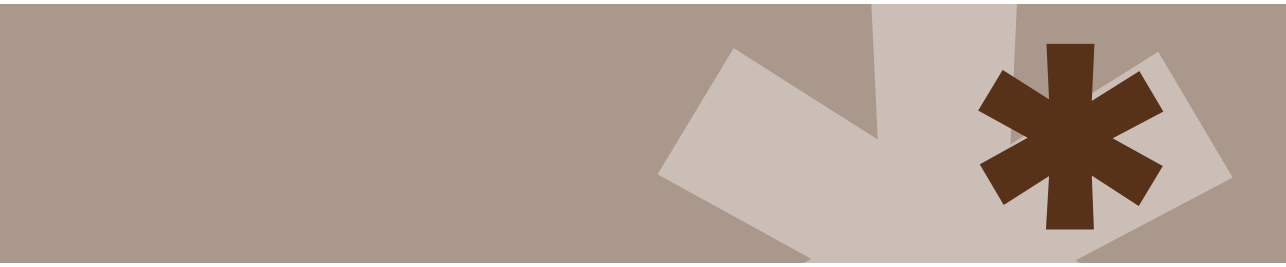
APPENDICES



Summary in Dutch

Samenvatting

De studies die in dit proefschrift worden gepresenteerd, zijn opgezet ter evaluatie van het effect van hormonale behandeling, oestrogenen gecombineerd met progestagenen en in het bijzonder tibolone, op het seksueel functioneren van postmenopauzale vrouwen met een seksuele disfunctie, zoals een verminderde seksuele interesse en/of een verminderd seksueel verlangen.
Om deze algemene vraagstelling te kunnen beantwoorden hebben wij een aantal aspecten nader in kaart gebracht met de bedoeling de juiste invalshoek te vinden om dit project op te zetten. De volgende subonderzoeksvragen werden hiertoe gedefinieerd:

1. Welke mening hebben postmenopauzale vrouwen ten aanzien van seksualiteit na de overgang en hoe denken (behandelend) artsen hierover?
2. Wat is een correcte en wetenschappelijk juiste benadering met betrekking tot de opzet van farmacologische interventie studies voor seksuele disfunctie bij vrouwen?
3. Wat is het effect van tibolone, gecombineerde oestrogenen met progestageen in verschillende toedieningsvormen en raloxifene (een selectieve oestrogen receptor modulator) op het seksueel functioneren bij postmenopauzale vrouwen?
4. Wat is het netto androgeen effect van tibolone op het seksuele functioneren bij postmenopauzale vrouwen met een seksuele disfunctie?

De doelstelling van de studies beschreven in dit proefschrift was om bij te dragen aan de huidige wetenschappelijke kennis over de rol van hormonale behandeling op het seksueel functioneren van vrouwen na de overgang en te zoeken naar farmacotherapeutische behandelmogelijkheden welke passen in een multidisciplinaire en tevens praktische aanpak bij vrouwen met seksuele problemen.

Hoofdstuk 4

Seksueel welbevinden na het 50e levensjaar: een Europees onderzoek onder vrouwen en artsen

Dit hoofdstuk beschrijft welke mening en attitude vrouwen hebben ten aanzien van seksualiteit na de overgang en wat hun eigen ervaringen zijn. Daarnaast is ook de mening en houding van artsen betreffende seksualiteit rond de middelbare leeftijd bepaald middels vergelijkbare vragen. Zes Europese landen participeerden in het onderzoek en in totaal werden meer dan 3000 postmenopauzale vrouwen en 600 artsen, gespecialiseerd in de behandeling van overgangsklachten, geïnterviewd. De meerderheid van de vrouwen (67%) gaf aan symptomen te ervaren die van invloed waren op het seksueel welbevinden zoals vaginale droogte en/of pijn en/of een verminderde seksuele interesse en seksueel verlangen. Dit had een negatieve invloed op de levenskwaliteit en de relatie met hun partner. Voor hen was de overgang en 'ouder worden' de belangrijkste oorzaak voor het verminderde seksleven. Seks werd als minder plezierig ervaren maar veel

vrouwen bleven seksueel actief, ondanks het veelvuldig voorkomen van seksuele problemen.
61% van de ondervraagde vrouwen vond seks net zo belangrijk als voor de overgang en een even zo groot aantal gaf aan hun leven meer te zullen genieten als hun 'seks-drive' zou zijn zoals voorheen. Ondanks een verminderde seksuele interesse en/of seksueel verlangen, was de meerderheid van de vrouwen tevreden over hun seksuele relatie. Vaginale droogte of (oppervlakkige) dyspareunie werd niet gezien als een belangrijke factor van invloed op de levenskwaliteit of seksualiteit. Voor de meeste vrouwen waren de seksuele problemen niet van dien aard of omvang, dat ze daarvoor behandeld zouden willen worden. Echter, 35% zou, als een medicijn beschikbaar zou zijn om seksuele problemen te verhelpen, overwegen dit te nemen.
De meeste vrouwen hadden het gevoel dat ze eerder hun seksuele problemen zouden bespreken als hun arts het onderwerp ter sprake zou brengen. Daartegenover stond dat één derde van de artsen van mening was, dat het bespreken van seksuele problemen taboe is en één derde vond het zelfs bezwaarlijk om seksuele problemen met oudere patiënten te bespreken. Ook werd het vóórkomen van een verminderd seksueel verlangen en seksuele interesse bij vrouwen door artsen onderschat, terwijl daarnaast het vóórkomen van vaginale droogte en dyspareunie overschat werd als oorzaak van seksuele problemen na de overgang.
Wij concluderen dat vrouwen en artsen seksuele problemen na de overgang verschillend zien: het voorlichten van zowel vrouwen als artsen betreffende seksualiteit lijkt één van de cruciale peilers te blijven om seksuele problemen gerelateerd aan de overgang op te lossen alvorens een behandeling te starten.

Hoofdstuk 5

Seksuele tevredenheid en farmacologische interventie: een kritische Review van de geneesmiddelenstudies voor vrouwelijk seksueel disfunctioneren

Dit hoofdstuk adresseert de huidige status van wetenschappelijk onderzoek naar vrouwelijke seksuele disfunctie. Recent verrichtte gerandomiseerde en gecontroleerde geneesmiddelen studies werden hiertoe gereviewed om te bepalen wat de hiaten zijn bij het vinden van een juiste onderzoeksbenadering. De beperkingen van deze studies zijn hiertoe samengevat evenals de betekenis van de uitkomsten van deze studies voor de klinische praktijk. De belangrijkste uitkomst van onze studie was dat een standaard methodologie voor wetenschappelijk onderzoek in dit vakgebied ontbreekt. De bepalende en tevens beperkende factoren zijn vooral de grote verschillen in de inclusie criteria en de verschillen in de meetmethode om veranderingen in seksueel functioneren vast te stellen. Onderzoek naar vrouwelijk seksueel disfunctioneren is een zich ontwikkelend vakgebied; zeer recent zijn nog nieuwe voorstellen gedaan voor de definitie van seksuele disfunctie bij vrouwen en voor een algemeen aanvaard responsmodel voor vrouwelijke seksualiteit. Om behandeleffecten van welke interventie dan ook op seksueel functioneren te kunnen meten moet eerst vast staan, welk

effect voor een vrouw eigenlijk van betekenis is. Er dient opheldering te komen over de volgende onderwerpen alvorens nieuwe interventiestudies voor vrouwelijke seksuele disfunctie te starten:
Een universeel geaccepteerde methode moet bepaald worden om vrouwelijke seksuele disfunctie te definiëren. Daaruit voortvloeiend moet er overeenstemming bereikt worden over de bepalende inclusie- en exclusie criteria evenals voor de belangrijkste uitkomstparameters ter evaluatie van de effectiviteit van farmacotherapie. De doelstellingen voor onderzoek moeten een afspiegeling zijn van klinisch relevante uitkomsten en tevens worden ingebed in een bio-psycho-sociaal seksueel responsmodel voor vrouwen.

Hoofdstuk 6

Effecten van tibolone en raloxifene op levenskwaliteit en seksueel functioneren

Dit hoofdstuk vergelijkt de effecten van tibolone en raloxifene op de levenskwaliteit, seksualiteit en vaginale atrofie bij gezonde, oudere postmenopauzale vrouwen met een verminderde botdichtheid (osteopenie). Hiertoe werd een prospectief dubbelblind onderzoek verricht bij 308 vrouwen (gemiddelde leeftijd 66 jaar) die gedurende twee jaar behandeld werden met tibolone of raloxifene. Gezondheidsgerelateerde levenskwaliteit werd gemeten met behulp van de Women's Health Questionnaire (WHQ), het seksueel functioneren middels Mc Coy Female Sexuality Questionnaire (MFSQ) en vaginale atrofie middels het bepalen van de karyopycnotische index (KI) en vaginale maturatie index. In de groep vrouwen die tibolone gebruikten werd een trend gezien naar een verbeterde de gezondheidsgerelateerde levenskwaliteit, waarbij de WHQ-waarden de normwaarden vastgesteld voor premenopauzale vrouwen benaderden, hetgeen voorafgaand aan de studie als klinisch relevant werd gedefinieerd. Daarentegen liet de groep vrouwen die behandeld werd met raloxifene een trend zien richting een slechtere levenskwaliteit volgens de WHQ. Een aantal WHQ domeinen, namelijk die betreffende het seksuele gedrag, gevoel van vrouwelijkheid en aantrekkelijkheid en van opvliegers, vertoonden in de tibolone groep een significante verbetering vanaf baseline vergeleken met de raloxifene groep.
Slechts de helft van de vrouwen in de studie had de McCoy seksualiteitsvragenlijst ingevuld. De belangrijkste oorzaak hiervoor was de afwezigheid van seksuele activiteit. Er kon geen significant verschil gemeten worden tussen de tibolone en de raloxifene groep in de totale score van de McCoy vragenlijst, noch in de afzonderlijke domein scores behalve die van de respons van de vagina ("vaginal lubrication") (p=0.037). Dit verschil was ook te zien vaginale maturatie index en karyopycnotische index, welke verbeterden in de tibolone groep en niet in de raloxifene groep.
Een post-hoc analyse van de afzonderlijke vragen van de McCoy liet een significante verbetering zien in de tibolone groep vergeleken met de raloxifene groep voor de volgende onderdelen: seksuele fantasieën, gevoel van seksuele opwinding en een vermindering van pijn tijdens de coïtus.
Beide behandelingen werden evengoed verdragen en er deden zich geen ernstige bijwerkingen voor betreffende het cardiovasculaire en/of cerebrovasculaire systeem.

Wij concluderen dat tibolone behandeling oudere postmenopauzale een trend inzet richting een verbetering van de levenskwaliteit en seksualiteit en dat raloxifene behandeling geen toegevoegde waarde heeft op deze uitkomstparameters.

Hoofdstuk 7

Effecten van tibolone vergeleken met een lage dosering orale E_2/NETA op urogenitale klachten, seksualiteit en kwaliteit van leven bij postmenopauzale vrouwen: resultaten van een gerandomiseerd, dubbel blind gecontroleerde studie

In dit hoofdstuk worden de effecten van tibolone vergeleken met een laag gedoseerde, E_2/NETA tablet (1mg/0.5mg) op de seksuele functie, urogenitale klachten en levenskwaliteit bij postmenopauzale vrouwen. Hiertoe werd gedurende 1 jaar een multi-center, gerandomiseerd, dubbel blind vergelijkend onderzoek uitgevoerd. Verschillende vragenlijsten werden gebruikt om de therapie respons te meten: voor seksuele functie werd de McCoy vragenlijst gebruikt, de WHQ voor gezondheid gerelateerde levenskwaliteit en de symptomenlijst voor urogenitale klachten (de Local UroGenital Complaint Scale).
572 postmenopauzale vrouwen met een leeftijd tussen de 45 en 65 jaar werden geïncludeerd. Beide behandelingen lieten na 48 weken een gunstig effect zien doordat niet alleen de algemene levenskwaliteit verbeterde, maar ook het seksueel functioneren en de urogenitale klachten. Tibolones gunstige effect op het seksuele functioneren was echter meer uitgesproken en vooral meetbaar in de groep vrouwen die op baseline geïdentificeerd waren met seksuele problemen. In de tibolone groep werd voor de totale studie populatie een significante verbetering in de McCoy score vastgesteld ten opzichte van de E_2/NETA groep ($p=0.038$). Dit was ook het geval voor het afzonderlijk McCoy domein betreffende de seksuele interesse. Verder liet het WHQ domein "tevredenheid met de seksuele relatie" een klinisch relevante verbetering zien bij de vrouwen die met tibolone waren behandeld, hetgeen niet vastgesteld kon worden in de E_2/NETA groep.

Hoofdstuk 8

Tibolone en transdermale E_2/NETA voor de behandeling van seksuele disfunctie bij postmenopauzale vrouwen: resultaten van een gerandomiseerde, actief-gecontroleerde studie

Dit hoofdstuk adresseert specifiek de effecten van tibolone bij postmenopauzale vrouwen met een seksuele disfunctie. Omdat wij een wetenschappelijk juiste vergelijking wilden maken, verrichtten wij een gerandomiseerde dubbel blinde studie waarin de effecten van tibolone gedurende 24 weken onderzocht werden tegen de E_2/NETA pleister als actief vergelijkend middel. Hiermee werden tegelijkertijd de indirecte effecten op de seksuele functie als gevolg van het verlichten van climactiele klachten ondervangen. De primaire doelstelling van de studie was om verschillen vast te stellen tussen beide behandel groepen in de samengestelde score van de "Female Sexual Function Index" (FSFI) bestaande uit het domein seksuele opwinding, seksueel verlangen en seksuele

tevredenheid. Secundaire uitkomstparameters waren, onder andere, de scores van de "Female Sexual Distress Scale" (FSDS) en de frequentie van "fijn vrijen" (seksuele gebeurtenissen die voor de vrouw naar tevredenheid waren), vastgesteld middels het bijhouden van een dagboek.
In totaal werden 403 vrouwen met een gemiddelde leeftijd van 56 jaar geïncludeerd. In de per-protocol analyse, welke bestond uit de groep vrouwen die therapie trouw waren geweest gedurende de studie en die niet een partner hadden die gedurende de studie als gevolg van bijvoorbeeld ziekte niet meer seksueel actief kon zijn, werd in de tibolone groep een significant grotere toename van de FSFI scores vastgesteld dan in de E_2/NETA pleister groep (p=0.036 voor de samengestelde FSFI score en p=0.025 voor de totale FSFI score). In de intent-to-treat analyse kon dit verschil niet worden waargenomen. Aan het eind van de studie werd er voor beide groepen een vergelijkbare toename gezien in de "fijn vrijen"-frequentie van 3 naar 4 keer per maand. Ook de FSDS scores verbeterden significant ten opzichte van de baseline waarden en waren vergelijkbaar voor de twee behandelgroepen. Van belang achtten wij de significante afname in het "afhouden van seksuele activiteit op initiatief van de partner" in de tibolone groep vergeleken met de E_2/NETA groep (-45% vs. -28%; p<0.001). Behandeling met tibolone resulteerde in een significante reductie van de serum waarden van het geslachtshormoonbindend eiwit (SHBG) en een toename in de vrije testosteron spiegel. In de E_2/NETA groep was dit niet het geval. Echter, er werd geen correlatie gevonden tussen gemeten geslachts hormoon spiegels en het seksueel functioneren.
In het algemeen was het voorkomen van bijwerkingen laag en vergelijkbaar tussen de twee behandelgroepen, alhoewel significant meer vrouwen in de E_2/NETA groep uit de studie vielen vanwege onregelmatig vaginaal bloedverlies.
Wij concluderen dat, ondanks dat beide behandelingen resulteerden in een significante verbetering van de seksuele functie, behandeling met tibolone naar waarschijnlijkheid eerder zal leiden tot een herstel van de seksuele functie dan de E_2/NETA pleister en dat tibolone daarnaast ook beter verdragen wordt.

Hoofdstuk 9

Verdraagbaarheid van tibolone vergeleken met de E_2/NETA pleister bij postmenopauzale vrouwen met een seksuele disfunctie: uitkomsten van een gerandomiseerd onderzoek

Dit hoofdstuk beschrijft aspecten die te maken hebben met de verdraagbaarheid van tibolone vergeleken met de E_2/NETA pleister. De belangrijkste uitkomst is hierbij onregelmatig vaginaal bloedverlies. In de beschreven studie waarin tibolone word vergeleken met E_2/NETA betreffende de effectiviteit op seksuele disfunctie, was dit het co- primaire eindpunt. Vaginaal bloedverlies en doorbraakbloedingen ("spotting") werden door de deelneemsters aan de studie bijgehouden in een dagboek. Per 12-weekse periode werden de "bleeding and spotting rates" per behandelgroep vergeleken. Vrouwen werden alleen dan in de analyse per periode geincludeerd als ze therapie trouw waren geweest in die periode en als ze niet meer dan 10 dagen hadden

vergeten het dagboek in te vullen. Voor beide periodes gold, dat de vrouwen in de tibolone groep significant minder last hadden van onregelmatig vloeien vergeleken met de E_2/NETA pleister. In de eerste 12 weekse periode was de incidentie van vaginaal bloedverlies en/of spotting 16% in de tibolone groep en 56% in de E_2/NETA pleister groep ($p<0.001$) en in de tweede 12-weekse periode was dit respectievelijk 12% versus 51% ($p<0.001$). Aan het eind van de studie had 24% van de vrouwen in de tibolone groep tenminste één dag last gehad van vaginaal bloedverlies tegen 72% in de E_2/NETA groep ($p<0.001$).
Bijwerkingen zoals gevoelige of gespannen borsten of mastopathie kwamen significant meer voor in de E_2/NETA groep dan in de tibolone groep (11% vs. 4%; $p=0.015$). Over het algemeen was het voorkomen van bijwerkingen laag en vergelijkbaar tussen de twee groepen. Wij concluderen dat tibolone een significant beter bijwerkingen- en tolerantie profiel heeft in vergelijking met de E_2/NETA pleister als gevolg waarvan meer vrouwen de behandeling konden continueren.

Hoofdstuk 10

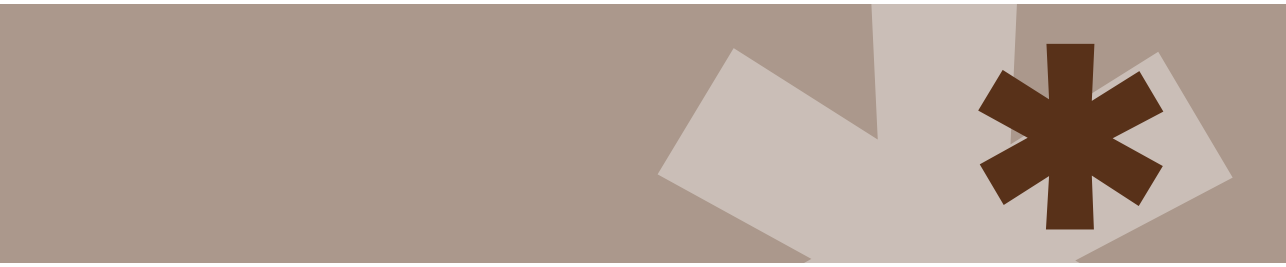
Farmacotherapie voor vrouwelijke seksuele disfunctie: exploratieve analyses van een gerandomiseerd onderzoek

Dit hoofdstuk vormt een gedetailleerde evaluatie van de studie uitkomsten beschreven in de voorgaande twee hoofdstukken. Vervolg analyses werden verricht, omdat algemeen bekend is dat dit soort onderzoek onderhevig is aan bias. De doelstelling van de huidige studie was, om inzicht te verkrijgen in potentiële "confounders" welke de studie resultaten beïnvloed zouden kunnen hebben. Een tweede doelstelling was hoe verder de gevonden data te interpreteren. Data van de FSFI, de FSDS en de WHQ werden hiervoor gebruikt en de analyses betreffende de screening en baseline data werden verricht op de beschikbare data van alle gescreende vrouwen respectievelijk alle geincludeerde vrouwen. Analyses betreffende de post-baseline data werden gedaan op de intent-to-treat populatie gebruik makend van de statistische benadering om de laatste gemeten data mee te nemen in de eind analyse ("Last Observation Carried Forward"). De uitkomsten van onze exploratieve analyses waren als volgt: de studie populatie was goed gedefinieerd en was een ware afspiegeling van een groep vrouwen met seksuele disfunctie. Er werd een klein, doch statistisch significant placebo effect waargenomen gedurende de 4-weekse run-in fase voorafgaand aan de studie hetgeen wellicht een significant placebo effect gedurende de studie periode teniet heeft gedaan. Er bestonden systematische verschillen in de gemiddelde FSFI scores per continent ($p=0.003$) en de FSDS en FSFI baseline scores waren afhankelijk van een aantal factoren zoals leeftijd, aantal jaren in de overgang en als grootste factor het land van herkomst. Het behandel effect kan redelijk consistent genoemd worden, omdat aan het eind van de studie de overlap van de uitkomsten op soortgelijke vragen in de WHQ en de FSFI groter was dan aan het begin van de studie gemeten middels de Somer's D coefficient (waarde: 0.50).
Wij houden daarom vast aan onze initiële conclusie dat tibolone in vergelijking met de E_2/NETA pleister, consistent het seksueel functioneren, verbetert bij vrouwen met een seksuele disfunctie.

Hoofdstuk 11

Algemene beschouwing

Europese vrouwen van middelbare leeftijd ervaren de menopauze als een levensfase welke seksuele veranderingen met zich meebrengt die op zichzelf van (negatieve) invloed kunnen zijn op hun persoonlijke leven. Echter, culturele normen en waarden evenals de ideeën rondom ziekte en gezondheid beïnvloeden de perceptie van deze seksuele veranderingen en ook de behoefte aan behandeling. Eén derde van de vrouwen zou open staan voor farmacologische behandeling als dit zou helpen om seksuele problemen op te lossen. Echter, uitleg en counseling, het liefst door een arts, blijft een van de cruciale elementen in een multidimensionele benadering van seksuele problematiek. Het (indirecte) effect van hormonale behandeling met oestrogenen al dan niet gecombineerd met progesteron, in het bijzonder in de transdermale toedienings-vorm, op de seksuele functie is aanzienlijk hoewel oudere postmenopauzale vrouwen wellicht minder voordeel hiervan ondervinden. Als farmacotherapie geïndiceerd is, moet tibolone als middel van eerste keus overwogen worden bij de behandeling van post-menopauzale vrouwen met seksuele problemen of seksuele disfunctie daar zowel de effectiviteit en de verdraagbaarheid nu voldoende is vastgesteld.



Measurement tools used in this thesis

Women's Health Questionnaire
McCoy Sexuality Questionnaire
Femal Sexual Distress Scale
Female Sexual Function Index

The Women's Health Questionnaire (WHQ)

Please indicate how you are feeling now, or how you have been feeling THE LAST FEW DAYS, by putting a tick in the correct box in the answer to each of the following items:

	Yes, definitely	Yes, sometimes	No, not much	No, not at all
1. I wake early and then sleep badly for the rest of the night	❑	❑	❑	❑
2. I get very frightened or panic feelings for apparently no reason at all	❑	❑	❑	❑
3. I feel miserable and sad	❑	❑	❑	❑
4. I feel anxious when I go out of the house on my own	❑	❑	❑	❑
5. I have lost interest in things	❑	❑	❑	❑
6. I get palpitations or a sensation of "butterflies" in my stomach or chest	❑	❑	❑	❑
7. I still enjoy the things I used to	❑	❑	❑	❑
8. I feel life is not worth living	❑	❑	❑	❑
9. I feel tense or "wound up"	❑	❑	❑	❑
10. I have a good appetite	❑	❑	❑	❑
11. I am restless and can't keep still	❑	❑	❑	❑
12. I am more irritable than usual	❑	❑	❑	❑
13. I worry about growing old	❑	❑	❑	❑
14. I have headaches	❑	❑	❑	❑
15. I feel more tired than usual	❑	❑	❑	❑
16. I have dizzy spells	❑	❑	❑	❑
17. My breasts feel tender or uncomfortable	❑	❑	❑	❑
18. I suffer from backache or pain in my limbs	❑	❑	❑	❑
19. I have hot flushes	❑	❑	❑	❑
20. I am more clumsy than usual	❑	❑	❑	❑

	Yes, definitely	Yes, sometimes	No, not much	No, not at all
21. I feel rather lively and excitable	❑	❑	❑	❑
22. I have abdominal cramps or discomfort	❑	❑	❑	❑
23. I feel sick or nauseous	❑	❑	❑	❑
24. I have lost interest in sexual activity	❑	❑	❑	❑
25. I have feelings of well-being	❑	❑	❑	❑
26. I have heavy periods (please omit if no periods at all)	❑	❑	❑	❑
27. I suffer from night sweats	❑	❑	❑	❑
28. My stomach feels bloated	❑	❑	❑	❑
29. I have difficulty in getting off to sleep	❑	❑	❑	❑
30. I often notice pins and needles in my hands and feet	❑	❑	❑	❑
31. I am satisfied with my current sexual relationship (please omit if not sexually active)	❑	❑	❑	❑
32. I feel physically attractive	❑	❑	❑	❑
33. I have difficulty in concentrating	❑	❑	❑	❑
34. As a result of vaginal dryness sexual intercourse has become uncomfortable (please omit if not sexually active)	❑	❑	❑	❑
35. I need to pass urine/water more frequently than usual	❑	❑	❑	❑
36. My memory is poor	❑	❑	❑	❑

37. Is it very difficult for you to cope with any of the above symptoms? YES/NO. If so, which ones:

McCoy Female Sexuality Questionnaire (MFSQ-SF)

McCoy Female Sexuality Questionnaire, Short-Form (MFSQ-SF)© 1 / 2

Instructions: Please answer the following questions in terms of your experience during the last 4 weeks. Please read each statement carefully and indicate to what extent each one applies to you.

1. Are you satisfied with your present frequency of sexual activity?

☐ Extremely unsatisfied ☐ ☐ ☐ Neither satisfied nor unsatisfied ☐ ☐ ☐ Extremely satisfied

2. How often have you had sexual thoughts or fantasies during the last 4 weeks?

☐ None of the time ☐ ☐ Once a week ☐ ☐ Once a day ☐ ☐ More than 10 times a day

3. How enjoyable has sex been for you?

☐ Not at all enjoyable ☐ ☐ ☐ Moderately enjoyable ☐ ☐ ☐ Very enjoyable

4. How often during sex have you felt aroused or excited (for instance increased heartbeat / flushing / vaginal wetness / heavy breathing etc.)?

☐ None of the time ☐ ☐ ☐ About half the time ☐ ☐ ☐ Every time

5. How often have you had an orgasm (climax) during sex?

☐ None of the time ☐ ☐ ☐ About half the time ☐ ☐ ☐ Every time

6. How often have you suffered from a lack of vaginal lubrication (wetness) during sex?

☐ None of the time ☐ ☐ ☐ About half the time ☐ ☐ ☐ Every time

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Female Sexual Distress Scale (FSDS)

Instructions

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and indicate the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST **30 DAYS** INCLUDING TODAY. Indicate only one number for each item, and take care not to skip any items. If you change your mind, record your change carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: Personal responsibility for your sexual problems.

NEVER	0
RARELY	1
OCCASIONALLY	2
FREQUENTLY	3
ALWAYS	4

HOW OFTEN DIDYOU FEEL:

1.	Distressed about your sex life	0 1 2 3 4
2.	Unhappy about your sexual relationship	0 1 2 3 4
3.	Guilty about sexual difficulties	0 1 2 3 4
4.	Frustrated by your sexual problems	0 1 2 3 4
5.	Stressed about sex	0 1 2 3 4
6.	Inferior because of sexual problems	0 1 2 3 4
7.	Worried about sex	0 1 2 3 4
8.	Sexually Inadequate	0 1 2 3 4
9.	Regrets about your sexuality	0 1 2 3 4
10.	Embarrassed about sexual problems	0 1 2 3 4
11.	Dissatisfied with your sex life	0 1 2 3 4
12.	Angry about your sex life	0 1 2 3 4

Female Sexual Function Index (FSFI)©

INSTRUCTIONS:
These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions, the following definitions apply:

- Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.
- Sexual intercourse is defined as penile penetration (entry) of the vagina.
- Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?
❑ = Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?
❑ = Very high
❑ = High
❑ = Moderate
❑ = Low
❑ = Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?
❑ = No sexual activity
❑= Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?

❑ = No sexual activity
❑ = Very high
❑ = High
❑ = Moderate
❑ = Low
❑ = Very low or none at all

5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?

❑ = No sexual activity
❑ = Very high confidence
❑ = High confidence
❑ = Moderate confidence
❑= Low confidence
❑ = Very low or no confidence

6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

❑ = No sexual activity
❑ = Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

7. Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?

❑ = No sexual activity
❑ = Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?

❑ = No sexual activity
❑ = Extremely difficult or impossible
❑ = Very difficult
❑ = Difficult
❑ = Slightly difficult
❑ = Not difficult

9. Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

❑ = No sexual activity
❑ = Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

❑ = No sexual activity
❑ = Extremely difficult or impossible
❑ = Very difficult
❑ = Difficult
❑ = Slightly difficult
❑ = Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

❑ = No sexual activity
❑= Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

❑ = No sexual activity
❑ = Extremely difficult or impossible
❑ = Very difficult
❑ = Difficult
❑ = Slightly difficult
❑ = Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

❑ = No sexual activity
❑ = Very satisfied
❑ = Moderately satisfied
❑ = About equally satisfied and dissatisfied
❑ = Moderately dissatisfied
❑ = Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?

❑ = No sexual activity
❑ = Very satisfied
❑ = Moderately satisfied
❑ = About equally satisfied and dissatisfied
❑ = Moderately dissatisfied
❑ = Very dissatisfied

15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

❑ = Very satisfied
❑ = Moderately satisfied
❑ = About equally satisfied and dissatisfied
❑ = Moderately dissatisfied
❑ = Very dissatisfied

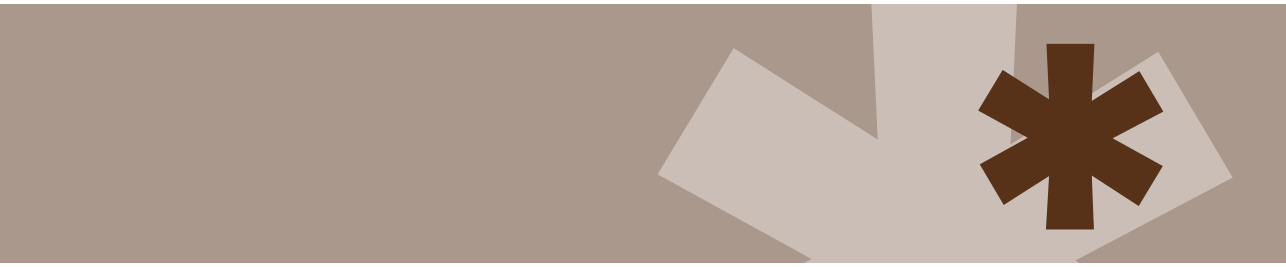
16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?
❑ = Very satisfied
❑ = Moderately satisfied
❑ = About equally satisfied and dissatisfied
❑ = Moderately dissatisfied
❑ = Very dissatisfied

17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?
❑ = Did not attempt intercourse
❑ = Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

18. Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?
❑ = Did not attempt intercourse
❑ = Almost always or always
❑ = Most times (more than half the time)
❑ = Sometimes (about half the time)
❑ = A few times (less than half the time)
❑ = Almost never or never

19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?
❑ = Did not attempt intercourse
❑ = Very high
❑ = High
❑ = Moderate
❑ = Low
❑ = Very low or none at all

Thank you for completing this questionnaire.



Curriculum Vitae

Esmé Nijland was born the eldest of three girls in Haaksbergen, the Netherlands on the 19th of June 1970. After finishing grammar school, she studied Medicine at the Free University of Amsterdam and graduated cum laude. She received her medical degree in 1998. After residencies in orthopaedics and gynaecology, she chose to pursue her professional career in the pharmaceutical industry. She held several positions there, including that of Clinical Research Physician at Eli Lilly and Director International Medical Services at Organon. Just recently she has made another career move because of her broad interest in health care and the birth of her daughter. She now works as a physician in a pain management clinic in her home base of Twente.

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List of Abbreviations

AE	: Adverse Event
AFUD	: American Foundation of Urologic Diseases
BDI	: Beck Depression Inventory
BISF-W	: Brief Index Sexual Functioning-Women
CE	: Conjugated Estrogens
CES-D	: Center for Epidemiologic Diseases-Depression Scale
CS	: Composite Score
CSES	: Changes Sexual Energy Scale
CSFQ-F-C	: Changes in Sexual Functioning Questionnaire-Female
CV	: Coefficients of Variation
DHEAS	: Dihydro Epi Androsteendione Sulphate
DSFI	: Derogatis Sexual Functioning Inventory
E_2	: Estradiol
ED	: Erectile Dysfunction
FIEI	: Female Intervention Efficacy index
FOD	: Female Orgasm Disorder
FSAD	: Female Sexual Arousal Disorder
FSD	: Female Sexual Dysfunction
FSDS	: Female Sexual Distress Scale
FSFI	: Female Sexual Function Index
FSH	: Follicle Stimulating Hormone
GEQ	: Global Efficacy Questions
HSDD	: Hypoactive Sexual Desire Disorder
HT	: Hormone therapy
HRQoL	: Health related Quality of Life
ITT	: Intent-To-Treat
KI	: Karyopycnotic Index
LOCF	: Last Observation Carried Forward
LSC	: Life Satisfaction Questionnaire
LUGCS	: Local Urogenital Complaint Scale
LVUT	: Last Value Under Treatment
MFSQ	: McCoy Female Sexuality Questionnaire
MPA	: Medroxy Progesterone Acetate
MSIQ	: Sexual Interest Questionnaire
NETA	: Norethisterone
PDS	: Personal Distress Scale
PEQs	: Personal Experience Questionnaire
PFSF	: Profile of Sexual Functioning
PGWBI	: Psychological General Well-Being Index
PP	: Per Protocol
RCT	: Randomized Controlled Trial

SAE	: Serious Adverse Event
SAL	: Sexual Activity Log
SAQ	: Self Administered Questionnaires
SDM	: Structured Diagnostic Method
SERM	: Selective Estrogen Receptor Modulator
SFQ	: Sexual Function Questionnaire
SHBG	: Sex Hormone Binding Globulin
SSRI	: Selective Serotonin Reuptake Inhibitor
SSSR	: Sabbatsberg Sexual Self Rating scale
STEAR	: Selective Tissue Estrogen Activity Regulator
T	: testosterone
TVUS	: Trans Vaginal Ultra Sound
VM	: Vaginal Maturation
VPA	: Vaginal Pulse Amplitude
WHQ	: Women's Health Questionnaire